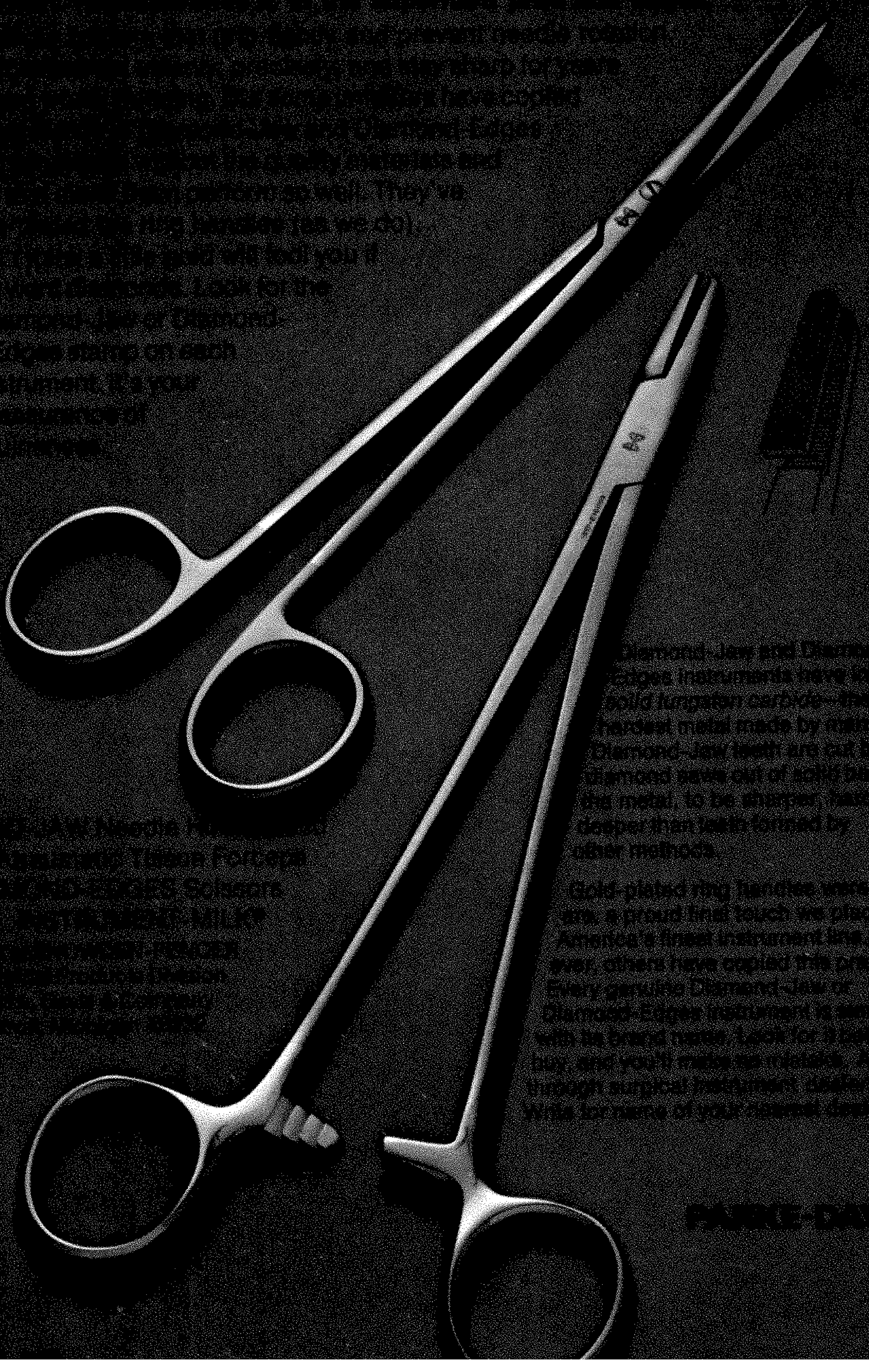

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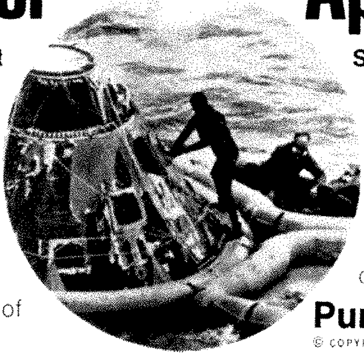

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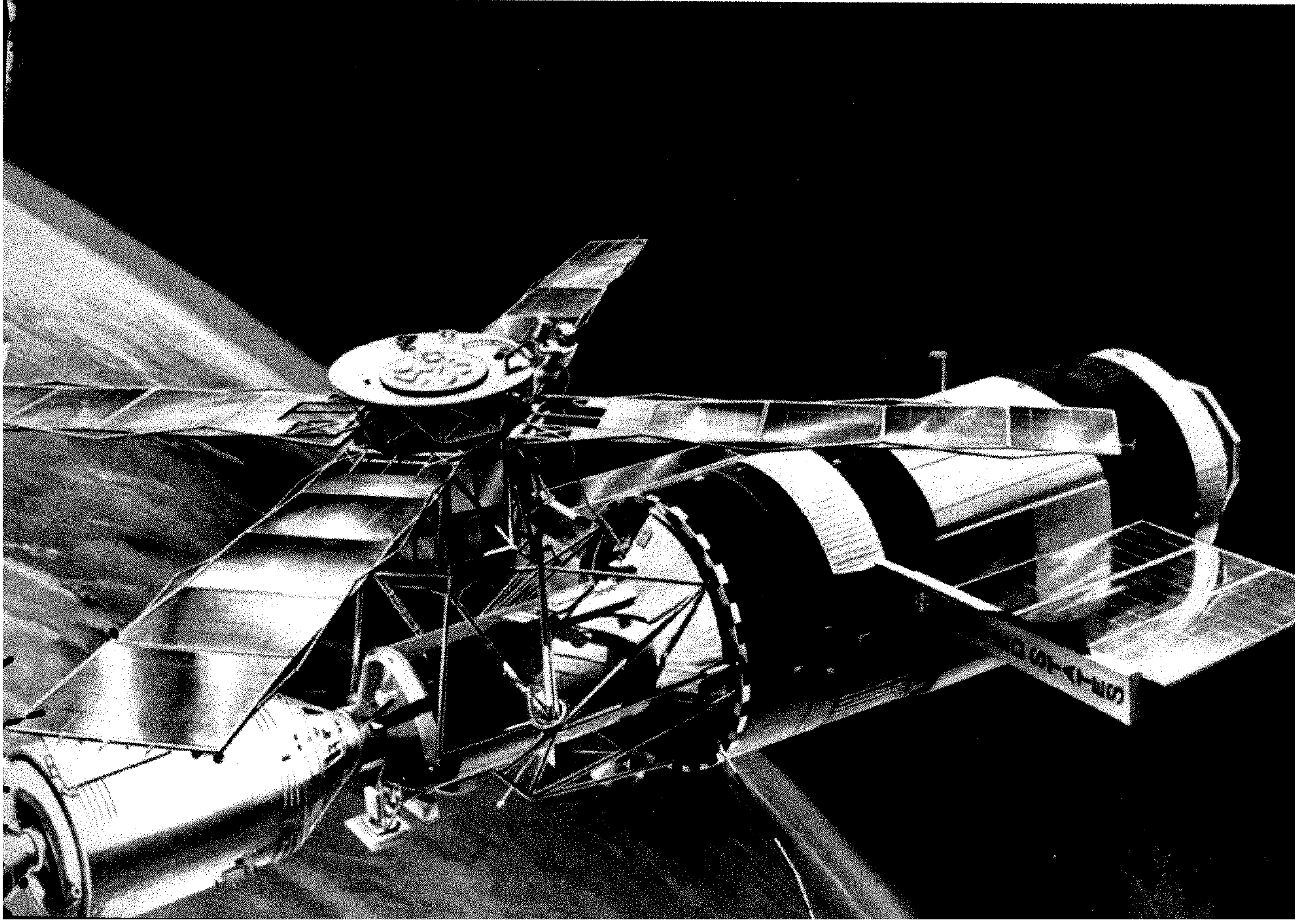

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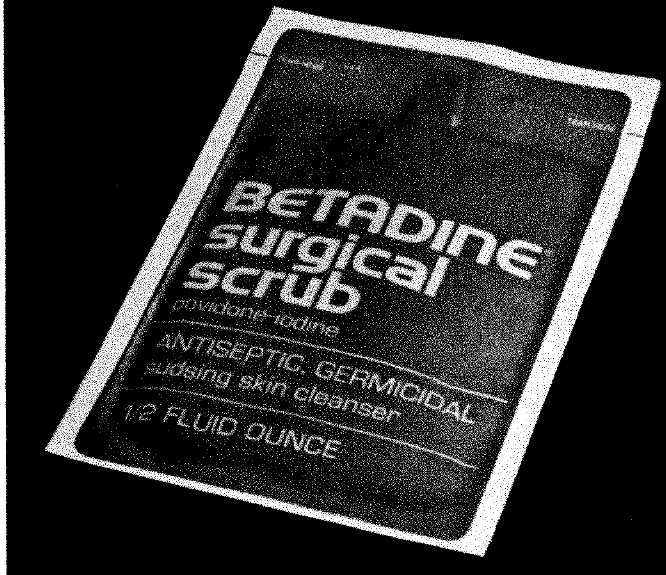

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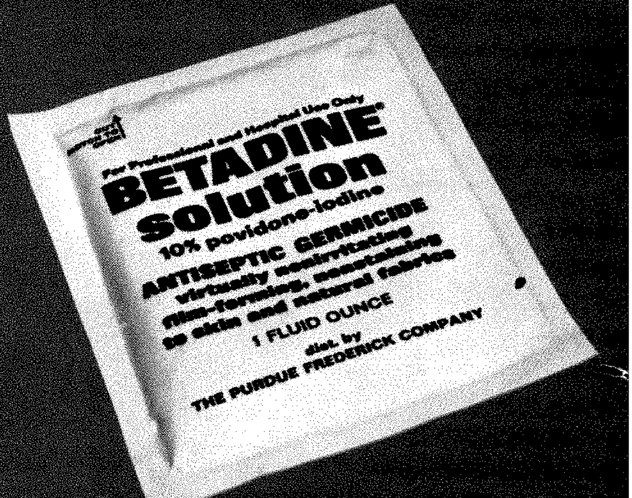
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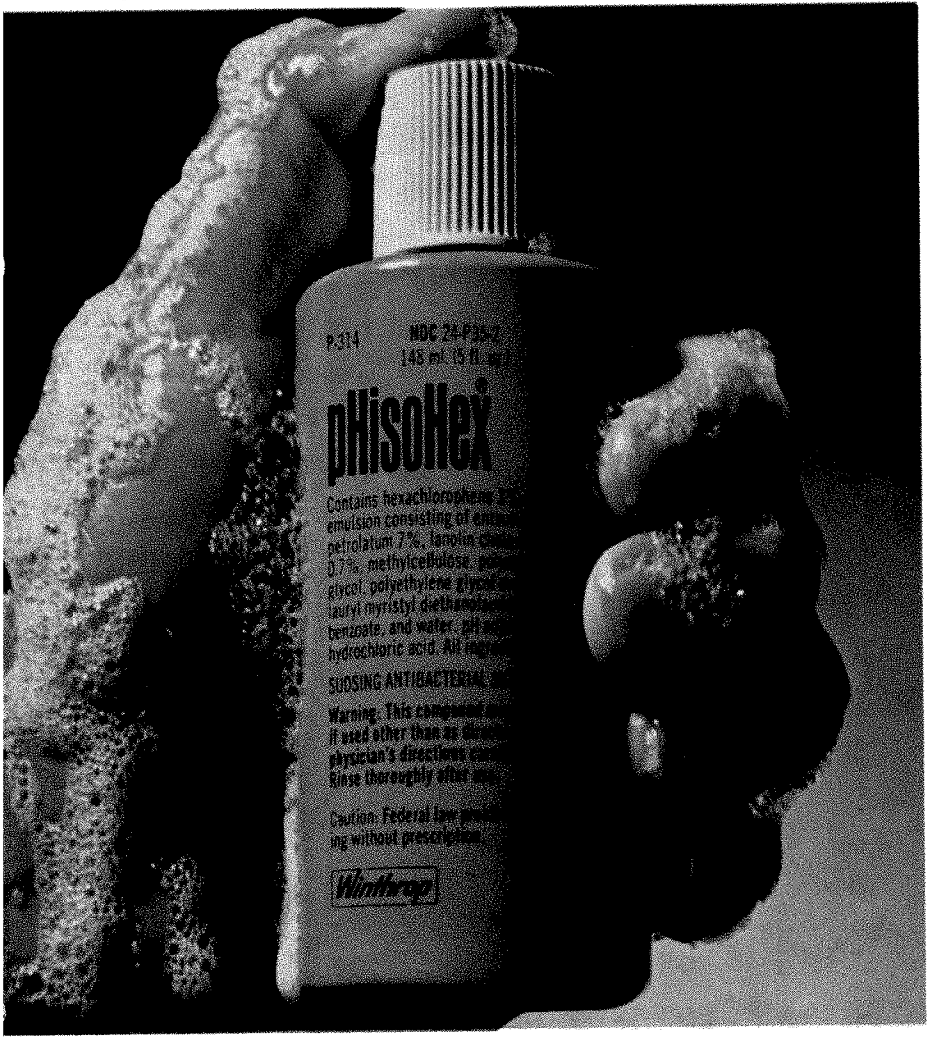

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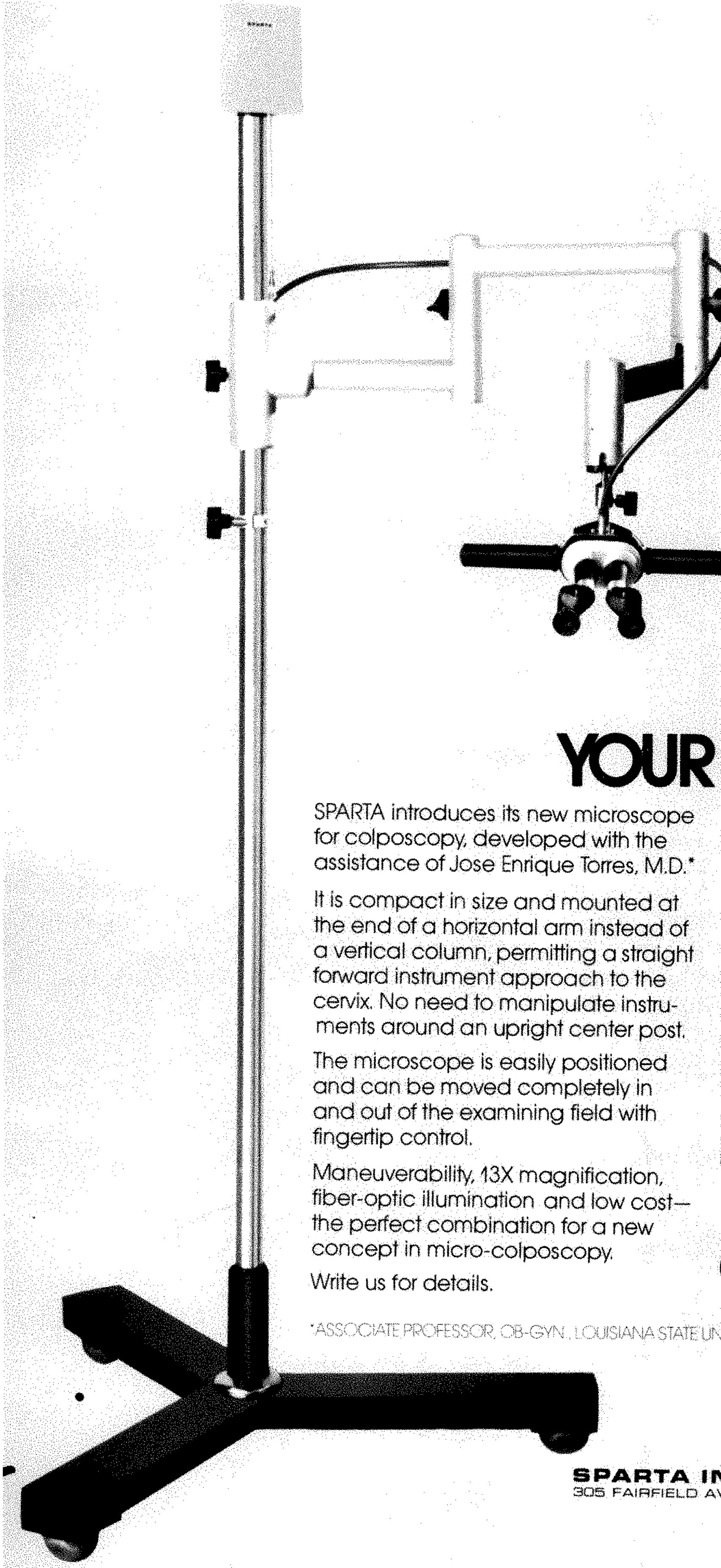

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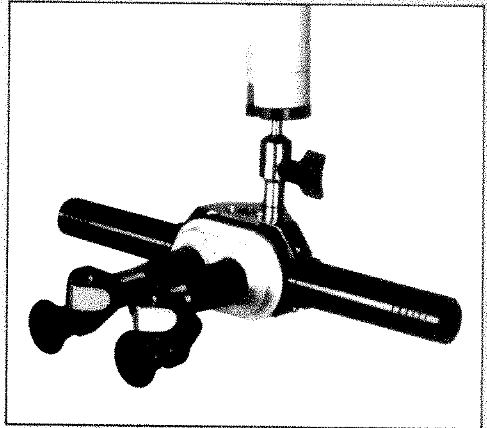

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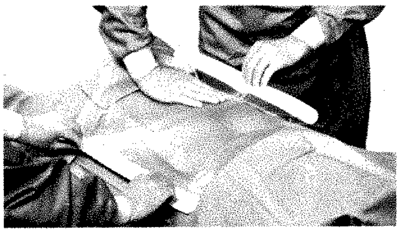

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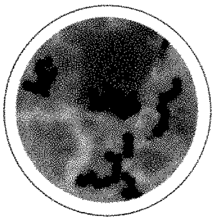

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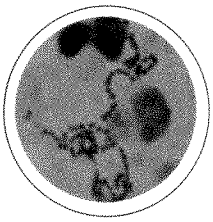

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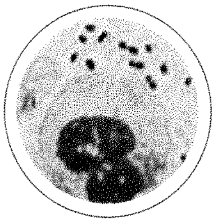

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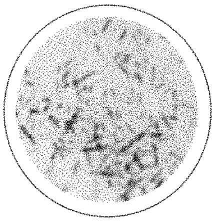


Anaerobic bacteria —(Including species of *Bacteroides, Fusobacterium, Propionibacterium, Eubacterium, Actinomyces, Peptococcus, Peptostreptococcus,* microaerophilic streptococci and *Clostridium.*)

Septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess; infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal-cuff infection; empyema, anaerobic pneumonitis, lung abscess; skin and soft-tissue infections.

For further prescribing information, please see last page of this advertisement.

STERILE SOLUTION

Cleocin® PO4

clindamycin phosphate injection, Upjohn

An injectable antibiotic for staph, strep, pneumococci...

*susceptible strains of the

There are good reasons to consider Cleocin Phosphate (clindamycin phosphate injection) as the initial drug when indicated in moderate to severe infections caused by susceptible strains of staph, strep** and pneumococci.

Clinically and bacteriologically, clindamycin has proved effective in patients with penicillin-resistant staphylococcal infections. Cleocin PO4 is effective against penicillinase-producing staphylococci. However, organisms resistant to clindamycin have been encountered and sensitivity testing should be performed.

Cleocin PO4 is useful in patients who are sensitive to penicillin. Rare cases of sensitivity to clindamycin resulting in maculopapular rash and urticaria have been reported and, as with all antibiotics, it should be used cautiously in atopic patients. However, clindamycin's only demonstrable cross antigenicity is with lincomycin. Thus it can fill a need for both penicillin-sensitive patients and those with penicillin-resistant pathogens.

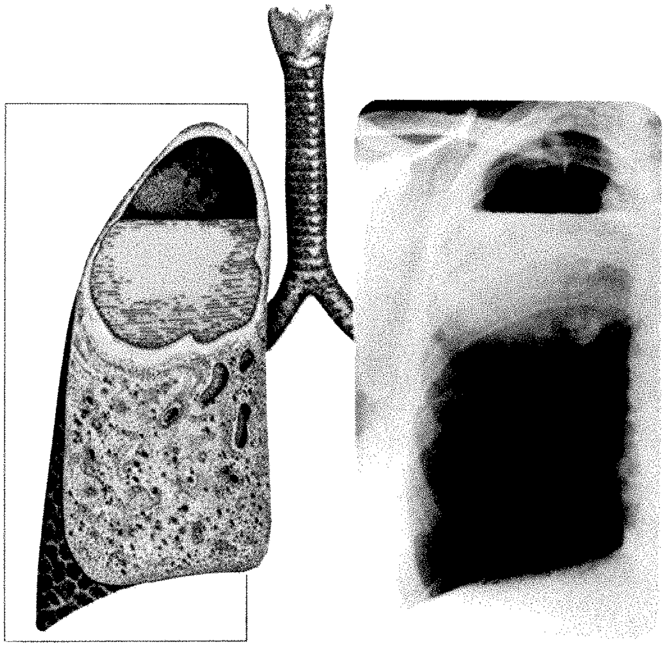
In occasional individuals Cleocin PO4 may cause gastrointestional symptoms including nausea, vomiting and diarrhea. CASES OF SEVERE AND PERSISTENT DIARRHEA HAVE BEEN REPORTED AND HAVE AT TIMES NECESSITATED DISCONTINUANCE OF THE DRUG. THIS DIARRHEA HAS BEEN OCCASIONALLY ASSOCIATED WITH BLOOD AND MUCUS IN THE STOOL AND HAS AT TIMES RESULTED IN ACUTE COLITIS. A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

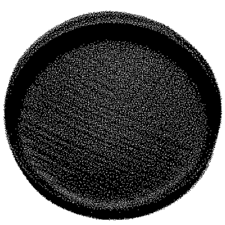
Useful as initial therapy... with a bonus. Cleocin PO4 is indicated for more than the treatment of susceptible gram-positive organisms.** It has the bonus of activity against anaerobes. For these obscure and potentially lethal pathogens, it may merit early consideration.

Anaerobes: ubiquitous opportunists. Anaerobes are the dominant population group among the resident flora of the human body. They are abundant in the oropharynx, female genital tract, and in the gut where they constitute 95% of normal fecal flora, out-numbering *Escherichia coli* 1,000 to 1.

Except for *Clostridium*, which became notorious during World War I, anaerobes have often been dismissed as harmless saprophytes. Only recently have they begun to be recognized as a major source of serious infection.

When trauma, surgery, or weakened bodily defenses allow them to spill into the peritoneal cavity, or invade the bloodstream or compromised tissue, they can become lethal opportunists.





When the medium has no message. Anaerobes are the most easily missed category of potentially pathogenic bacteria. Often their presence can only be inferred when a lesion that shows abundant bacteria on a Gram-stained slide yields an apparently sterile culture with routine aerobic methods.

Anaerobes require meticulous collection and special culture techniques. Even a brief exposure to air can kill many of them. Most are fastidious, and they may require as much as ten days' incubation to reveal their presence. In some busy laboratories, plates are discarded prematurely; in others, anaerobic cultures are rarely even made.

The problem of Bacteroides. *Bacteroides* are the most numerous of the anaerobic bacteria and the ones most frequently found in clinically significant anaerobic infections. *Bacteroides* species have been identified in approximately half of surgical infections caused by anaerobic organisms.

Although most *Bacteroides* species are sensitive to penicillin, a frequent exception is *Bacteroides fragilis*—the most commonly encountered pathogen in the genus. This, the most prevalent of anaerobic pathogens, has remained the most difficult to eradicate. Despite antibiotic therapy, *Bacteroides* septicemia has proved fatal in 30% to 40% of patients afflicted.

**Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal pharyngitis and its long-term prophylaxis of rheumatic fever.

For further prescribing information, please see last page of this advertisement.
A complete bibliography is available from The Upjohn Company.

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and anaerobes*

*pathogens indicated above

Improving the odds against anaerobes. In anaerobic infections the therapeutic significance of Cleocin PO$_4$ (clindamycin phosphate injection) is best recognized in the context of the seriousness of many of the infections successfully treated. All but one of the clinically and bacteriologically evaluatable patients in the pre-introductory study group had moderate to severe infections. Most had one or more complicating illnesses and, in many, host defenses were severely compromised by traumatic injuries, neoplastic disease, or radical surgery.

Anaerobic infections developed in many as a sequel to massive abdominal gunshot or stab wounds, multiple fractures, or surgery of the gastrointestinal or female genital tract.

Clinical diagnoses included septicemia, deep abscesses of the lungs and various sites in the abdominal cavity and female genital tract, and cases of peritonitis, empyema, endometritis, postsurgical vaginal-cuff infections and anaerobic pneumonitis. In many cases multiple antibiotic regimens, alone or in combination, had failed to control the infection before Cleocin PO$_4$ therapy was initiated.

Serum levels of clindamycin above the *in vitro* minimum inhibitory concentration for most indicated organisms can be readily achieved and maintained. The minimum inhibitory concentration *in vitro* for anaerobes is generally 1.6 mcg/ml or less.

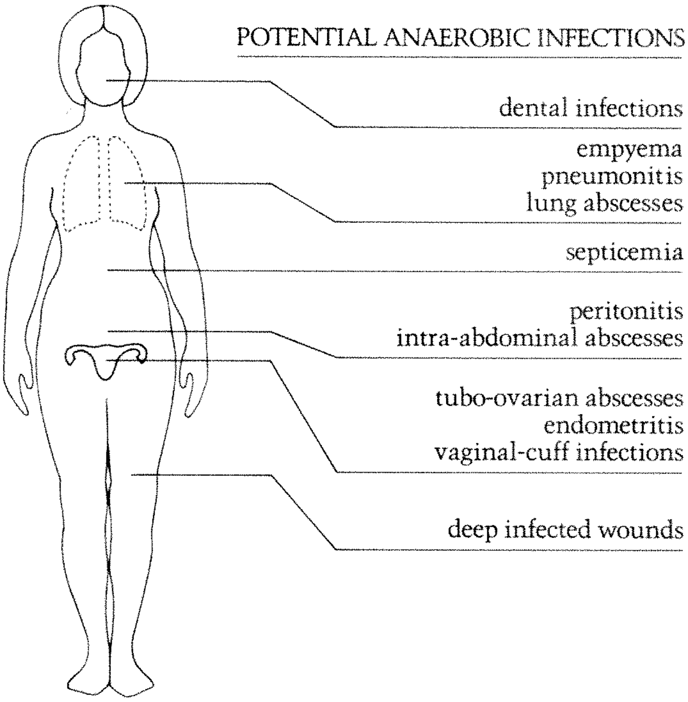
When you suspect an anaerobe. Cleocin PO$_4$ (clindamycin phosphate injection) is demonstrably effective in anaerobic infections. But with or without the availability of effective antibiotics, the principal problem in managing these infections is recognizing them.

A questioning mind and a sensitive nose are the first and second prerequisites, respectively. Deep necrotic lesions are a potential breeding ground for anaerobes, particularly if located near the oropharynx, the female genital tract, or the gut. Contamination from these areas enhances the risk of infection, as does compromised host resistance. A foul or fecal-smelling lesion or exudate suggests anaerobic infection. Organisms that are visible on the Gram-stained slide but fail to grow on conventional aerobic culture media may be anaerobes.

As with any infection, specimens for culturing and susceptibility testing should be collected before therapy begins. At present, since disc susceptibility testing with present methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility. In severe anaerobic infections, treatment may be started before a definitive diagnosis is made.

If it's a gram-positive coccal infection, there are several alternatives.

If you suspect an anaerobe, consider Cleocin PO$_4$.



Predictable serum levels… predictably maintained. Cleocin PO$_4$ is a water-soluble ester of clindamycin and phosphoric acid which hydrolyzes into biologically active clindamycin base within minutes of infusion. Peak serum concentrations of active antibiotic are reached in ten minutes following a 300 mg intravenous dose. With intra-muscular administration, peak levels are achieved within three hours in adults and one hour in children.

Serum levels of clindamycin above the *in vitro* minimum inhibitory concentrations for most indicated organisms can be maintained by administration of clindamycin phosphate every 8-12 hours in adults and every 6-8 hours in children, or by continuous intravenous infusion.

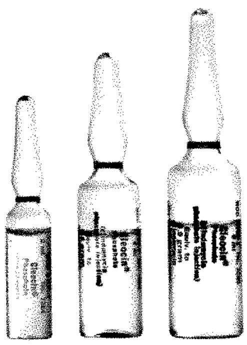
Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease. However, patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy. Elevations of serum transaminases have been observed during therapy with Cleocin PO$_4$ (clindamycin phosphate injection).

Cleocin PO$_4$ should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in the Dosage and Administration section of the prescribing information.

STERILE SOLUTION ●

Cleocin® PO4

clindamycin phosphate injection, Upjohn



Effective parenteral therapy against susceptible gram-positive cocci and anaerobes

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Description and Actions: Cleocin Phosphate is a water soluble phosphate ester of clindamycin. Clindamycin is a semisynthetic antibiotic which has greater *in vitro* potency than the parent compound lincomycin. While clindamycin phosphate is inactive, rapid *in vivo* hydrolysis converts it into the antibacterially active clindamycin.

Indications: Cleocin Phosphate is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Streptococci: Upper respiratory-tract infections (Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. Cleocin Phosphate is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cleocin Phosphate in the subsequent prevention of rheumatic fever are not available at present.); lower respiratory-tract infections; skin and soft-tissue infections; septicemia.

Staphylococci: Upper and lower respiratory-tract infections; skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Upper and lower respiratory-tract infections.

Anaerobic bacteria: Lower respiratory-tract infections such as empyema, anaerobic pneumonitis and lung abscess; skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal-cuff infection.

Adjunctive Therapy: In dental infections and in the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies to determine the causative organisms should be performed and their susceptibility to Cleocin tested.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: CASES OF SEVERE AND PERSISTENT DIARRHEA HAVE BEEN REPORTED AND HAVE AT TIMES NECESSITATED DISCONTINUANCE OF THE DRUG. THIS DIARRHEA HAS BEEN OCCASIONALLY ASSOCIATED WITH BLOOD AND MUCUS IN THE STOOLS AND HAS AT TIMES RESULTED IN AN ACUTE COLITIS.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between Cleocin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established. *Usage in Newborns and Infants:* When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable. *Usage in Meningitis:* Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of non-susceptible organisms—particularly yeasts. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin phosphate should not be injected intravenously as an undiluted bolus; it should be infused as directed in package insert. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy. In experimental animals, high doses of lincomycin IV have been shown to have neuromuscular blocking properties which are not reversed by neostigmine. Other animal studies have shown that there can be an additive effect or potentiation when lincomycin is given concurrently with d-tubocurarine. There are no studies to this effect with clindamycin phosphate; however, the possibility of this occurring with clindamycin phosphate should be kept in mind due to the chemical similarity of the drug.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. See also under WARNINGS. *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing. *Local Reactions:* Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How supplied: 2, 4 and 6 ml ampoules.

Caution: Federal law prohibits dispensing without prescription.

MED-B-1 (MCP-2) J-3532-9

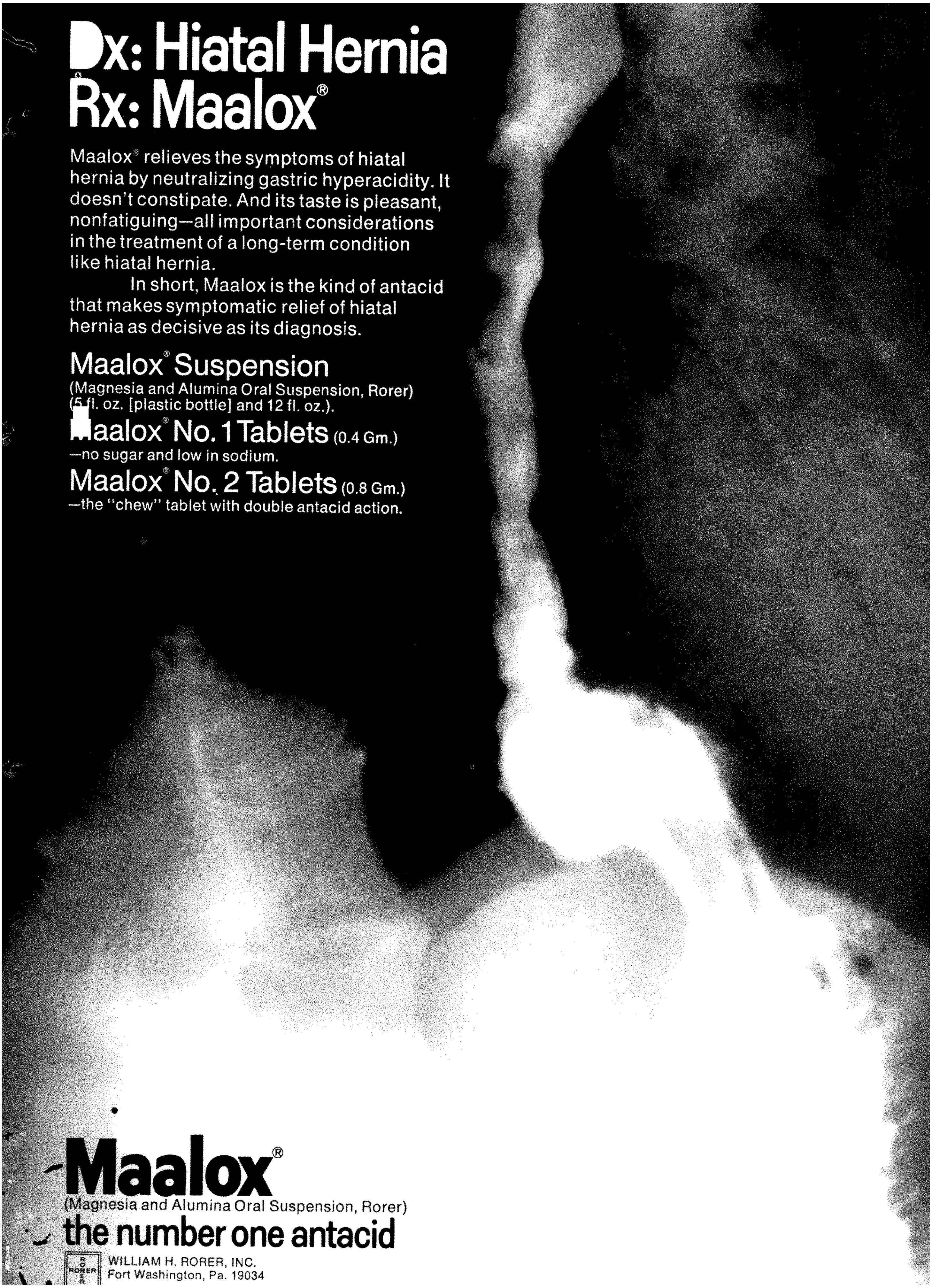
STERILE SOLUTION

Cleocin® PO4

clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE

The Upjohn Company



Dx: Hiatal Hernia
Rx: Maalox®

Maalox® relieves the symptoms of hiatal hernia by neutralizing gastric hyperacidity. It doesn't constipate. And its taste is pleasant, nonfatiguing—all important considerations in the treatment of a long-term condition like hiatal hernia.

In short, Maalox is the kind of antacid that makes symptomatic relief of hiatal hernia as decisive as its diagnosis.

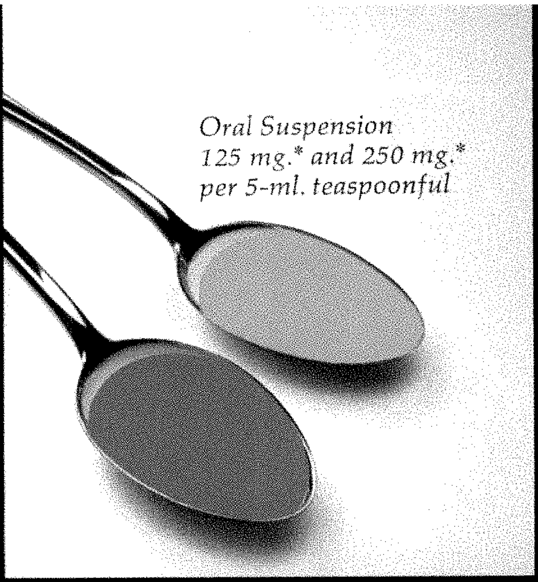
Maalox® Suspension
(Magnesia and Alumina Oral Suspension, Rorer)
(5 fl. oz. [plastic bottle] and 12 fl. oz.).

Maalox® No. 1 Tablets (0.4 Gm.)
—no sugar and low in sodium.

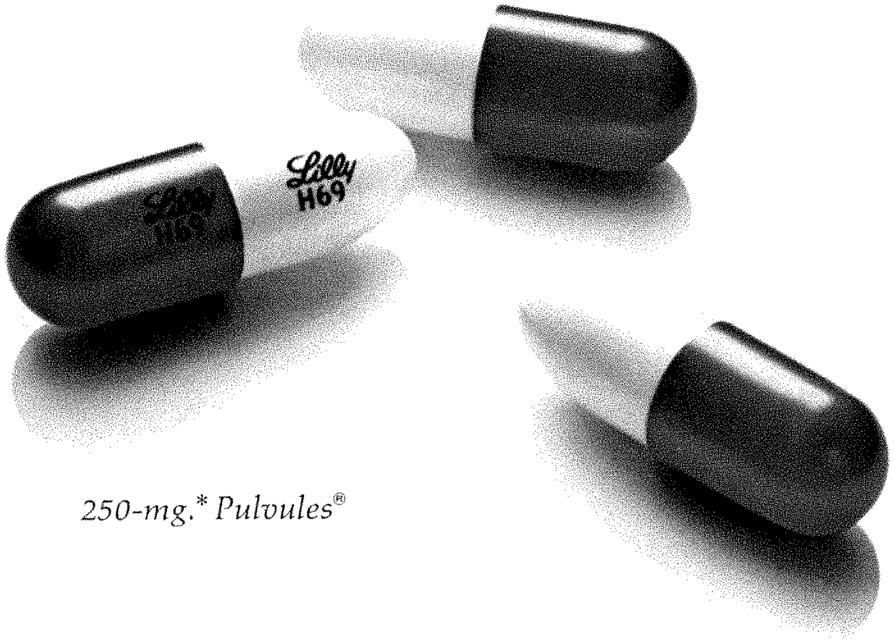
Maalox® No. 2 Tablets (0.8 Gm.)
—the "chew" tablet with double antacid action.

Maalox®
(Magnesia and Alumina Oral Suspension, Rorer)
the number one antacid

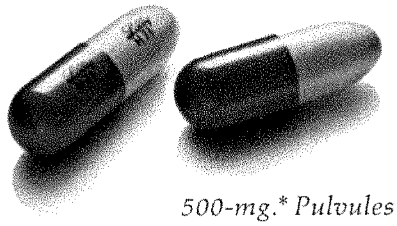
RORER
WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034



Oral Suspension
125 mg. and 250 mg.**
per 5-ml. teaspoonful



250-mg. Pulvules®*



500-mg. Pulvules*

Keflex®
cephalexin monohydrate

Lilly

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Additional information available
to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

**Equivalent to cephalexin*

ANNALS OF SURGERY

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Alterations in Ventilatory Function and Breathing Patterns Following Surgical Trauma

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OVER THE PAST DECADE, improved methods of cardiocirculatory resuscitation have enabled many patients to survive circulatory shock or other severe trauma. However, morbidity and mortality rates among such patients remain high, primarily as the result of the high incidence of pulmonary insufficiency.[14,16] By the time pulmonary insufficiency has become clinically detectable, the patient's course is precarious and sometimes irreversible. Thus it is important to elucidate the factors which contribute to the development of posttraumatic pulmonary insufficiency and to devise effective methods for detecting and interpreting early changes in pulmonary function. Such methods are essential for assessing and controlling the effectiveness of therapeutic and preventive measures.

The present study has utilized continuous spirometry to determine how 2 operations of differing magnitude influence the normal patterns of breathing and certain ventilatory parameters.

Studies in patients undergoing inguinal herniorrhaphy, a procedure which is accomplished with no major involvement of the abdominal muscles and peritoneum, were expected to show the effect of anesthesia, anxiety, pain, and possibly other factors usually associated with general surgery. On the other hand, the studies of patients with upper abdominal operations were designed to show the respiratory effects not only of the general factors, but also of pain and spasm involving upper abdominal and lower intercostal muscles and the diaphragm, and the effects of the ileus that follows intraperitoneal operations. The establishment of the nature and severity of the changes caused by surgical injury is a necessary first step in an investigation of whether such changes, if progressive over days, can lead to clinical pulmonary complications and possibly to pulmonary insufficiency.

Methods and Procedures

The canopy-computer-spirometry system used in this study, which has been described in detail previously,[20] is composed of a head canopy connected to a spirometer (Med-Science Co., Model 470) and an IBM 1130 computer. The canopy is a rigid transparent head chamber with a neck seal, ventilated by a continuous air stream which passes to carbon dioxide and oxygen analyzers. The spirometer connected to the canopy provides a breath-by-breath record of lung volume changes. Spirometry and gas exchange data are acquired and processed by the digital computer, which also controls the air flow to the canopy to produce a stable spirometer baseline position (baseline controller). Algorithms for quantifying each breath and for determining tidal volume, frequency and minute ventilation at evenly spaced points in time are executed by the computer. An accuracy of ±10 ml. in the tidal volume measurement is achieved for breathing frequencies in the range of 5–40 breaths per minute. The program excludes all tidal volumes less than 40 ml., since they have arbitrarily been considered too small to rep-

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resent a breath. The first 10 minutes of every run is also discarded since data obtained in this period may be variable due to the patient's adjustment to the system.

Twelve male patients between the ages of 25–70 readily consented to undergo the ventilatory measurements described above. In addition to routine hospital work-up, a short history was taken for each patient and a physical examination performed, focusing attention on the cardiopulmonary system. Also, in each case, the results of ECG, chest x-ray Hgb and Hct measurements were noted. Patients who had any findings suggestive of preexisting cardiopulmonary disease were not included in this study.

Six patients undergoing inguinal herniorrhaphy were studied 1–2 days preoperatively and on the first postoperative day; 6 patients undergoing upper abdominal operations were studied 1–2 days preoperatively and on the second postoperative day. All patients had general anesthesia for their operations. Care was taken to make sure that patients had not received any respiratory depressants for at least four hours before each measurement.

The results from a spirometry run included the breath-average value of tidal volume ($\bar{V}_T$) and the time-average values of frequency (f = total breaths/total duration of the run in minutes), carbon dioxide excretion* ($\dot{V}co_2$—ml/min) and oxygen uptake* ($\dot{V}o_2$—ml/min). The respiratory equivalents for carbon dioxide ($\dot{V}/\dot{V}co_2$) and oxygen ($\dot{V}/\dot{V}o_2$) were calculated from the time-average values of $\dot{V}$, $\dot{V}co_2$, and $\dot{V}o_2$.

All spirometry runs were conducted in the morning or midafternoon in a quiet room with the patient in recumbent position on a flat hospital bed. In each case runs of about 75 minutes were accomplished with minimal physical activity. There was an observer in the room with the patient at all times. During runs, patients were encouraged to listen to music of their choice as a deterrent to falling into a deep sleep, although most of them apparently dozed or slept for varying short intervals.

At the end of each 75 minute run, vital capacity (3 attempts) and the maximal breathing capacity (15 sec. duration) were determined.

In addition to spirometry runs performed on pre- and postoperative patients, runs were performed on another group of 5 normal male volunteers, ranging in age from 26–50. These runs were done 2–5 times for each volunteer on different days, under conditions similar to those of the patient runs, but lasting for 120 minutes.

Results

Since the subject-to-subject variations in respiratory parameters due to age, body habitus, or other factors were expected to be large relative to the changes produced by these operations, the ratios of the postoperative parameter values to the corresponding preoperative values were calculated for each subject. Thus the postoperative over preoperative ratios are the basic results from each pair of pre- and postoperative runs, so that each patient served as his own control. A postoperative/preoperative ratio of unity or close to unity indicates that the operation had no effect.

The averages and standard deviations of these ratios were calculated for each group studied. It should be noted that, of the 9 pairs of runs for the 5 normal subjects, several pairs were obtained from the same subject.

To assess the significance of the changes in parameter ratios, the group averages were compared with each other using a two-sample unequal variance t-test. If it could be assumed that there is no subject acclimatization to the canopy-computer-spirometer (CCS) system, then the average parameter ratios for the normal subjects should be unity, and the fact that they are not is attributed to random variations. Thus P values were calculated for both the normal variations in normal subjects and on the assumption that the average parameter ratios for the normal subjects were unity (Table 1 and 2).

The comparison of the inguinal herniorrhaphy patients with the normal subjects (Table 1) showed moderate (5–10%) increases in tidal volume, frequency, gas exchange rates, and respiratory equivalents, but these increases were not significant at the 95% level. The increases in V_T and f combined to increase minute ventilation by 14.7%, and thus was just significant at the 95% level. These results are expected,[10,17] and are consistent

TABLE 1. *Average Postoperative/Preoperative Parameter Ratios—Normal Subjects and Inguinal Herniorrhaphy Patients*

	V_T	f	$\dot{V}$	$\dot{V}CO_2$	$\dot{V}O_2$	$\dot{V}/\dot{V}CO_2$	$\dot{V}/\dot{V}O_2$
Normal Subjects (N = 9)							
Average	.97	1.05	1.01	.98	.97	1.03	1.03
Standard Deviation	.026	.022	.024	.012	.008	.005	.011
Inguinal herniorrhaphy (N = 6)							
Average	1.06	1.10	1.16	1.03	1.04	1.14	1.13
Standard Deviation	.011	.017	.023	.007	.006	.031	.024
% Difference	8.9	4.7	14.7	4.7	6.3	10.8	8.6
p	.12	$>.50$	.05	.20	.10	.10	.13
p*	.22	.10	.04	$>.50$	.22	.06	.06

* p-value computed assuming normal subject averages equal to 1.
V_T = tidal volume
f = frequency, respiratory rate
$\dot{V}$ = minute ventilation
$\dot{V}_{CO_2}$ = CO_2 production
$\dot{V}_{O_2}$ = O_2 consumption
$\dot{V}/\dot{V}_{CO_2}$ = the amount of air moved per minute for removal of 1 L. CO_2; respiratory equivalent.
$\dot{V}/\dot{V}_{O_2}$ = respiratory eqiuvalent based on O_2 consumption.

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* The calculation of time-average $\dot{V}co_2$ and $\dot{V}o_2$ from evenly-spaced values has been described previously[20]

TABLE 2. *Average Postoperative/Preoperative Parameter Ratios—Normal Subjects and Upper Abdominal Operation Patients*

	V_T	f	$\dot{V}$	$\dot{V}CO_2$	$\dot{V}O_2$	$\dot{V}/\dot{V}CO_2$	$\dot{V}/\dot{V}O_2$
Normal subjects (N = 9)							
Average	.97	1.05	1.01	.98	.97	1.03	1.03
Standard Deviation	.026	.022	.024	.012	.008	.005	.011
Upper Abdominal Operation (N = 6)							
Average	.78	1.54	1.15	1.04	1.08	1.11	1.08
Standard Deviation	.14	.52	.18	.12	.15	.18	.22
% Difference	−19.7	46.9	13.4	5.6	10.3	8.4	4.7
p	.02	.04	.08	.21	.09	.16	.50
p*	.01	.03	.07	.50	.17	.09	.22

* p-value computed assuming normal subject ratio averages equal to 1.

with the idea that pain and emotional stress tend to produce hyperventilation. It is also worth noting that, for the normal subjects, none of the average parameter ratios varied by more than 5% from the value of unity that is expected if there is no acclimitization to the canopy, and if the respiratory parameters measured are essentially constant over days or weeks. Thus, mild, but potentially significant, changes in respiration and gas exchange produced by injury or illness may be detectable using the canopy-computer-spirometry system.

The upper abdominal operation patients, in contrast, showed (Table 2) on the average a 20% decrease in tidal volume, a 47% increase in frequency, and a 13% increase in minute ventilation. None of the other average ratios changed by more than 10%, and only the tidal volume and frequency changes were significant at the 95% level. In particular, the constancy of the respiratory equivalents offers one indication that overall lung function has not been impaired in the second postoperative day. These results also are in accord with previous findings.[10,15,17]

Tidal Volume Distribution

Since a run usually comprised 500 to 1500 breaths, it was possible to obtain reasonable estimates of the distribution of tidal volumes (per cent of breaths against tidal volumes during the total run period). Fig. 1 shows typical first and second run tidal volume distributions for normal subjects (no operation performed) and patients who underwent upper abdominal operations. Qualitatively it appears that for normal subjects the tidal volume distribution is stable from day to day, and that inguinal herniorrhaphy had no significant effect on the distribution curves. The upper abdominal operation, on the other hand, reduces the mean tidal volume, narrows the distribution, and markedly decreases the rate at which larger than normal breaths occur.

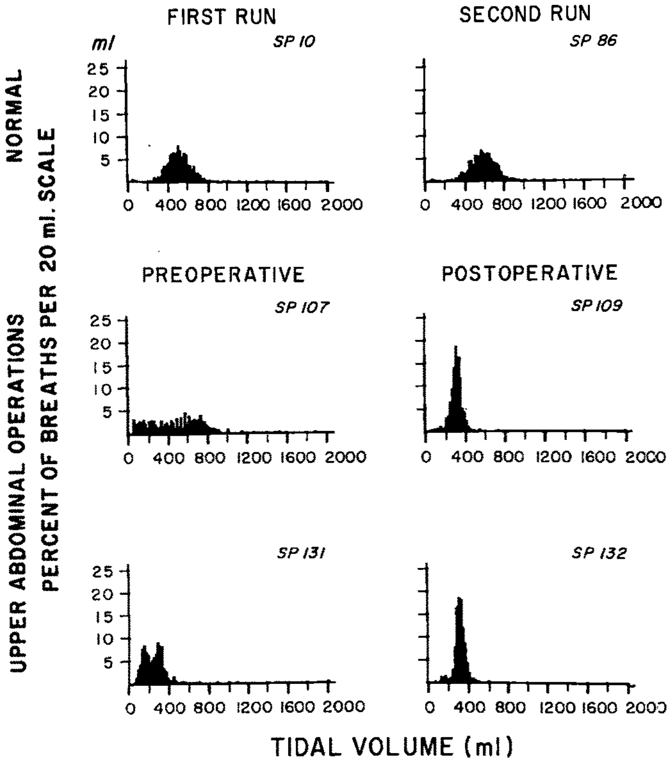

FIG. 1. Tidal volume distribution curves of normal are shown in upper first and second runs. The preoperative and postoperative upper abdominal operations (gastrectomy and cholecystectomy) are shown in the lower four graphs.

To confirm these observations quantitatively, the mean and standard deviation at each distribution were calculated, as were the fraction of breaths larger than 110%, 125%, 200%, and 300% of the preoperative mean tidal volume. For upper abdominal incision patients, it can be seen from Table 3 that the mean tidal volume is reduced by 20% (as shown above), and that the standard deviation of the distribution also drops by about 15%. While statistical tests of significance were not done because some of the assumptions on which the tests are based were not satisfied, the differences of the means are roughly equal to the standard deviations.

The most striking change in the tidal volume distribution, however, is the reduction in the number of breaths with larger than normal tidal volume. For the upper abdominal operations, for example, the fraction of breaths with tidal volume greater than 110% of the preoperative mean tidal volume ($\overline{V}_T$) decreased from 33% to 10%, a decrease from 18% to 1% was observed for breaths greater than 125% of $\overline{V}_T$. Upper abdominal operations abolished breaths, or sighs, greater than 200% and 300% of $\overline{V}_T$.

Oscillations

Most of the subjects, both preoperative patients and normal volunteers, demonstrated oscillations of tidal volume with respect to variations in volume. These

TABLE 3. *Average Values of Tidal Volume Distribution Parameters and Parameter Ratios*

	Mean Tidal Volume (ml)	Standard Deviation of Distribution (ml)	110% $\overline{V}_T$*	125% $\overline{V}_T$*	200% $\overline{V}_T$*	300% $\overline{V}_T$*
Normal Subjects (N = 5)						
First runs ± S.D.	423 ± 128	128 ± 98	18.4 ± 15	6.3 ± 9	1.4 ± 3	.17 ± .3
Second runs ± S.D.	402 ± 52	138 ± 56	24.2 ± 33	13.4 ± 21	0.9 ± 1	.30 ± .2
2nd/1st Ratio ± S.D.	1.00 ± .22	1.68 ± 1.4	2.64 ± 3.3	4.1 ± 4	2.9 ± 4	1.00 ± 1.7
Inguinal Herniorrhaphy (N = 5)						
Preop Runs ± S.D.	415 ± 70	132 ± 67	23.1 ± 14	8.2 ± 3	1.1 ± 1	.08 ± 5
Postop Runs ± S.D.	439 ± 67	130 ± 66	38.0 ± 17	12.9 ± 10	1.3 ± 2	.12 ± .57
Postop/Preop Ratio ± S.D.	1.06 ± .10	1.21 ± 1.0	3.89 ± 6	1.89 ± 1.8	2.34 ± 5	.12 ± .2
Upper Abdominal Operation (N = 6)						
Preop Runs ± S.D.	434 ± 183	170 ± 49	32.5 ± 12	17.6 ± 16	1.1 ± 1	.23 ± .2
Postop Runs ± S.D.	325 ± 78	132 ± 109	10.0 ± 22	.9 ± 2	0.0 ± 0	0.0 ± 0
Postop/Preop Ratio ± S.D.	.80 ± .2	.85 ± .3	.28 ± 6	.09 ± .1	0.0 ± 0	0.0 ± 0

* Percent of breaths with tidal volume greater than 110 to 300% of the preoperative average tidal volumes.

oscillations appeared as increasing and decreasing tidal volume variations occurring in cycles, at a rate of 1–3 cycles/min. (Fig. 2). There were also noticeable oscillations of the end-expiratory level "expiratory mid-position" among normal and preoperative patients.[20] In parts of several runs the "baseline controller" was turned off, but the oscillations were qualitatively unchanged, indicating that oscillations were neither caused nor reduced by the controller. When the baseline changes measured by the computer were plotted against time following computer elimination of "baseline controller" effect, sinusoidal oscillations similar to the oscillations in tidal volume variations were seen. The range of variation in the expiratory level was 100–300 ml. and, in the runs of several patients, the periodicity of oscillation was 1–3 cycles/min., as was the periodicity of the tidal volume variations, so that the tidal volume and expiratory baseline appeared to oscillate in phase. Only the postoperative abdominal cases showed a diminution of these oscillations (Fig. 3).

The postoperative vital capacity (VC) and maximal breathing capacity (MBC) appeared to decrease significantly following upper abdominal operations. However, most patients were unable to cooperate fully in vital capacity and maximal breathing capacity tests following surgery so that postoperative measurements of these parameters were considered unreliable.

Discussion

In the present study, only upper abdominal operations were shown to change the ventilatory parameters and breathing patterns significantly. These changes were primarily characterized by a restricted type of breathing with decreased tidal volumes and a markedly increased

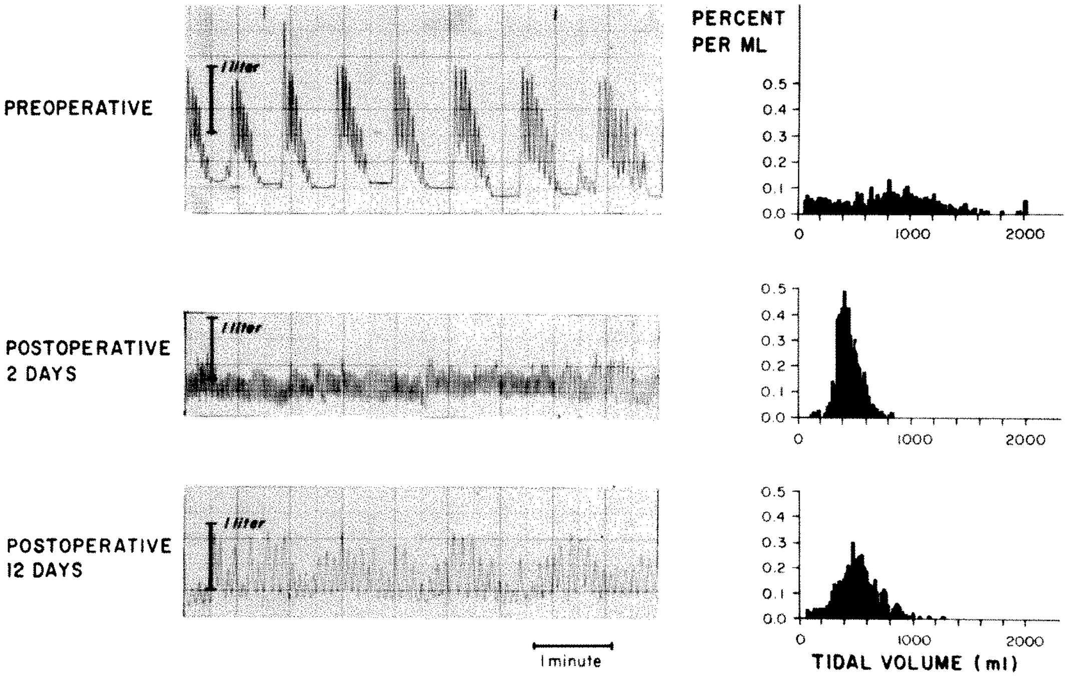

FIG. 2. Spirograms and the tidal volume distribution graphs of a 50 year-old–black male weighing 96 Kg., height 178 cm., BSA of 2.04 m² without any history of cardiopulmonary disease. He underwent an elective cholecystectomy without any significant clinical complication.

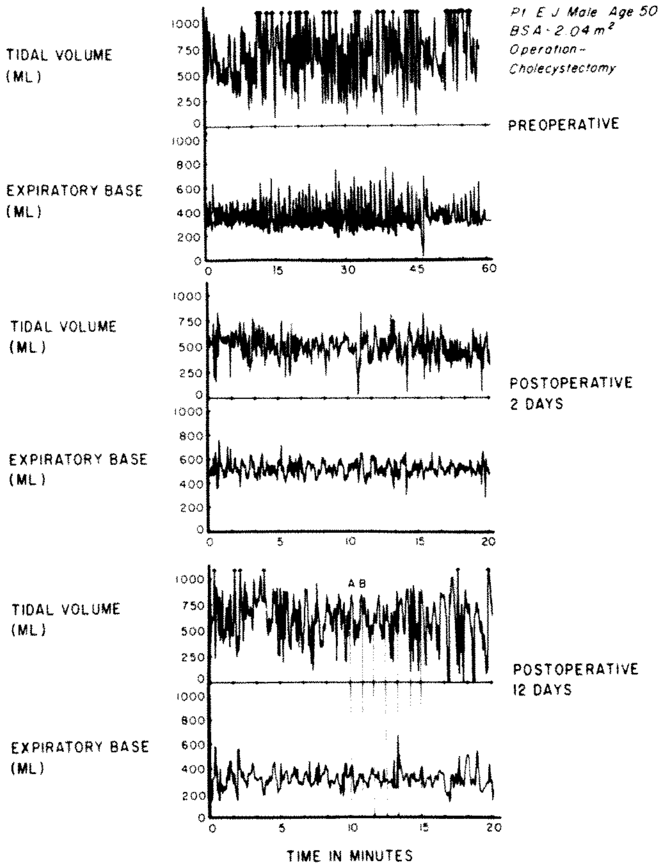

FIG. 3. Computer plotting of breath-by-breath variations of tidal volume (upper) and expiratory base (next lower) show phasic oscillations of tidal volume and expiratory base as in lines A and B.

respiratory rate. It is interesting that the normal respiratory rate of adult patients is commonly considered to be 20 breaths per minute and nursing charts often show a straight line at this value. The present study has shown that the normal rate is closer to 14 ± 4 breaths/min. and that rates as high as 25–30 breaths/min, which are sometimes hardly observable and often are not recorded, may be a significant indication of ventilatory change.

The increase in respiratory rate following upper abdominal operations or other major trauma has long been a subject for debate. Post-traumatic tachypnea could be the result of any one or any combination of the following: 1) increased metabolism; 2) hypoxic or hypercapnic or hydrogen ion (chemical) stimulation; 3) psychological (supratentorial) stimulation; 4) proprioceptive stimuli from the lungs or respiratory muscles. The present evidence indicates that the increased respiratory rate following abdominal operations probably is not a response to an increased oxygen demand since postoperative oxygen consumption is not significantly elevated.[11] Also, hypoxic stimulation is unlikely. The data of Latimer et. al. show that there is no statistically significant difference in the arterial oxygen saturation between preoperative and postoperative upper abdominal operations.[10] Dripps and Comroe[4] have shown that hypoxic stimulation does not occur at levels of oxygen saturation above 90 per cent. Joels and Neil[9] demonstrated that chemoreceptor stimulation occurs only at arterial oxygen tensions below 60 m.m. Hg. An earlier study[11] in this surgical unit had demonstrated that the arterial PO_2 after upper abdominal operations averaged 76.6 ± 4.1 and that there were no significant changes in the arterial PCO_2 or pH postoperatively. In addition, it is a common clinical observation[14] that most of these patients are in mild respiratory alkalosis and thus are not driven to tachypnea by accumulated CO_2. Furthermore, administration of oxygen and bicarbonate, with resulting elevations of PaO_2 above 100 and the pH, do not change this pattern of shallow rapid breathing.

The supratentorial or psychologic aspects of the postoperative response, although important, do not seem to be the cause of persistent postoperative or post-traumatic tachypnea. This is substantiated by 2 clinical observations. First, acute psychological stimuli which cause marked changes in rate and volume are generally transitory.[14] Secondly, some post-trauma comatose patients who appear to be subject to no definable psychologic stimulation, nevertheless demonstrate sustained tachypnea.

Although the general relationship of local pain and muscular spasm to the central nervous system registration of pain is not clear, it does appear that neuromuscular stimulation of the respiratory centers through afferent stimuli from the incision and its periphery, can alter the ventilatory parameters following trauma. The afferent pain and proprioceptive stimuli from abdominal muscles in spasm may be related to the stimulation of respiratory centers. Since abdominal muscles are innervated by the intercostal nerves (T_7 to T_{12}) there is an interplay between the abdominal muscles and the lower intercostal muscles. Pain and spasm in these muscles restrict the normal expansion of the thoracic cage and the normal motion of the diaphragm, causing a protective shallow breathing.

This restricted type of breathing, indicated by smaller tidal volumes and absence of large breaths and sighs, is the most likely cause of increased respiratory rate.[5] Mead's work[13] has strongly suggested that reflexly mediated increased frequency adjustments of respiration to restricted breathing are made possible by afferent vagal stimuli originating in the lungs. Therefore, it is reasonable to believe that in some postoperative and post-traumatic patients tachypnea may be the result of a restricted type of breathing which leads to the stimulation of stretch receptors within the lungs, and in turn to the stimulation of respiratory centers to a higher rate of respiration.

A decreased tidal volume similar to that which we observed was noted by Anscombe[1] under similar experimental conditions, in addition to the decreased vital capacity, decreased maximum expiratory rate and decreased maximum inspiratory rate. It is also interesting in this regard that Starr and Gilman[21] eliminated limitation of ventilation following surgery by use of an intercostal afferent nerve block, reducing the pain and spasm. In cases of major non-thoracic trauma occurring in Vietnam combat, Proctor[17] also showed significant decrease in tidal volume and significant increase in respiratory rate, with the combination resulting in minimal changes in minute ventilation. Herniorrhaphy under general anesthesia, however, did not significantly decrease the tidal volume and frequency, although minute ventilation was increased probably as the result of some pain and anxiety.

Many investigators have shown postoperative changes in f, V_T and $\dot{V}$. However, there has been no clarification of other aspects of breathing patterns. Bendixen[2] showed the presence of variations in tidal volumes and the presence of sighing as a normal breathing pattern in young adults. Goodman[7] reported periodic sustained oscillations of ventilation with time-dependent variations in normal volunteers.

Sighing (300% $\bar{V}_T$) occurred as 1% of all breaths among Bendixen's young adults, whereas sighing occurred in less than 0.3% of the total breaths among our preoperative and normal subjects.[23] The frequency of sighing was unchanged by inguinal herniorrhaphy, but upper abdominal incisions resulted in a complete abolition of the 200% $\bar{V}_T$ sighs and the 300% $\bar{V}_T$ sighs. These measurements also reveal that in normal breathing, oscillations in tidal volume do often occur cyclically as increasing and decreasing tidal volume variations at 1–3 cycles/min. Furthermore, the tidal volume distribution curves of normal volunteers and preoperative patients usually have a wide range of distribution which was significantly narrowed following upper abdominal operations (Figs. 1 and 2).

In addition to the oscillatory changes in tidal volume, oscillations of end-expiratory level were discernible in 75% of normal volunteers and preoperative patients. The baseline (expiratory mid-position) oscillations occurred at 1–3 cycles/min., and were in phase with the tidal volume oscillation (Fig. 3). It must be added that the patient in Figs. 2 and 3 represents an exaggerated form of this type of breathing. This pattern of breathing simulates HPB (hypersomnia with periodic breathing) that is often seen in the Pickwickian Syndrome.[12] However, this patient had no clinical features of this syndrome. Most other subjects and patients in this study did demonstrate tidal volume and baseline oscillations without periods of apnea. Greene and Coggeshall[8] reported oscillations of "expiratory position" with a body plethysmograph occurring in some normal subjects. Saunier[18] noticed similar oscillations in patients with bronchitis, and suggested that these oscillations represented oscillations of the functional residual capacity. This periodicity in breathing pattern in normal individuals has also been observed by Gillam;[6] however, its physiologic significance is still a conjecture. In the present study, these oscillations were less evident or absent following upper abdominal operations (Fig. 3).

Sighing, although not always present, is postulated as an important mechanism for alveolar inflation. However, an alternate means of accomplishing alveolar inflation may be the phasic oscillations of tidal volume and end-expiratory level which, at the peak of oscillation, represents large tidal volumes and elevated functional residual capacity occurring simultaneously, thereby simulating sighing.[23] Although the additive volumes of peak tidal volume and peak end-expiratory level may not reach the volume of a sigh, the slow build-up of FRC and transpulmonary pressure with superimposition of the largest values of the oscillating tidal volume may be important for alveolar inflation and alveolar recruitment.[19,22]

It is therefore possible that with absence of sighing and large breaths as well as diminution of tidal volume and the phasic oscillations of tidal volume and end-expiratory base, there would be incomplete inflation and recruitment of alveolar units leading to scattered micro-atelectasis. It has been suggested by Williams, Tierney and Parker[22] that "probably the alveolus cannot maintain a low surface tension for long without occasional large inflations which replenish the surface with surface-active material." With increasing surface tension in certain alveolar units, the fluid balance in and around such units may overcome the plasma oncotic pressure in capillaries and favor transudation through the pulmonary capillaries.[3] This may be one of the contributing factors in the development of the vicious cycle leading to the heavy lung syndrome of the post-traumatic pulmonary insufficiency.

Conclusions

Inguinal herniorrhaphy under general anesthesia does not produce any significant changes in ventilatory parameters and breathing patterns 24 hours postoperatively. However, upper abdominal operations produce statistically significant changes in ventilatory parameters: 20% decrease in tidal volume and 47% increase in respiratory rate. In addition, this restricted type of breathing markedly reduced the proportion of large breaths and eliminated sighing. Tidal volume and end-expiratory base oscillations seen in most preoperative patients were reduced or were not discernible following upper abdominal operations. It is suggested that this type of fixed volume rapid shallow breathing may lead to the development of scattered microatelectasis and if sustained long enough may be one of the initiating mechanisms in the development of post-traumatic pulmonary insufficiency in certain patients.

References

1. Anscombe, A. R.: Pulmonary Complications of Abdominal Surgery. Chicago, The Year Book Publishers Inc., 1957.
2. Bendixen, H. H., Smith, G. M. and Mead, J.: Patterns of Ventilation in Young Adults. J. Appl. Physiol., **19**:195, 1964.
3. Clements, J. A.: Pulmonary Edema and Permeability of Alveolar Membranes. Arch. Environ. Health, **2**:280, 1961.
4. Dripps, R. D. and Comroe, J. H.: The Effect of the Inhalation of High and Low Oxygen Concentrations on Respiration, Pulse Rate, Ballistocardiogram and Arterial Oxygen Saturation (Oximeter) of Normal Individuals. Am. J. Physiol., **149**:277, 1947.
5. Freedman, S. and Weinstein, S. A.: Effects of External Elastic and Threshold Loading on Breathing in Man. J. Appl. Physiol., **20**:469, 1965.
6. Gillam, P. M. S.: Patterns of Respiration in Human Beings at Rest and During Sleep. Bull. Physio-Pathol. Resp., **8**:1059, 1972.
7. Goodman, L.: Oscillatory Behavior of Ventilation in Resting Man. I.E.E.E. Trans on Bio. Med. Engin., **3**:82, 1964.
8. Greene, J. A. and Coggeshall, H. C.: Clinical Studies of Respiration: Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities on the Expiratory Position of the Chest in Man. Arch. Intern. Med., **52**:44, 1933.
9. Joels, N. and Neil, E.: The Excitation Mechanism of the Carotid Body. Brit. Med. Bull., **19**:21, 1963.
10. Latimer, R. G., Dickman, M., ClintonDay, W., Gunn, M. L. and Schmidt, C. D.: Ventilatory Patterns and Pulmonary Complications After Upper Abdominal Surgery Determined by Preoperative and Postoperative Computerized Spirometry and Blood Gas Analysis. Am. J. Surg., **122**: 622, 1971.
11. Lee, A. B., Kinney, J. M., Turino, G. and Gump, F. E.: Effects of Abdominal Operations on Ventilation and Gas Exchange. J. Nat. Med. Assoc., **61**:164, 1969.
12. Lugaresi, E., Coccogna, G., Mantovani, M., Ciriquotta, F., Ambrosetto and Baturii, P.: Hypersomnia with Periodic Breathing. Bull. Physio-Pathol. Resp., **8**:1103, 1972.
13. Mead, J.: Control of Respiratory Frequency. J. Appl. Physiol., **14**:669, 1959.
14. Moore, F. D., et al.: Posttraumatic Pulmonary Insufficiency. Philadelphia, W. B. Saunders Co., 1969.
15. Peters, R. M.: The Mechanical Basis of Respiration. Boston, Little, Brown and Company, 1969.
16. Pontappidan, H., Laver, M. B. and Geffin, B.: Acute Respiratory Failure in the Surgical Patient. Advan. Surg., **4**:163, 1970.
17. Proctor, H. J., Ballantine, T. V. N. and Broussard, N. D.: An Analysis of Pulmonary Function Following Non-Thoracic Trauma, with Recommendations for Therapy. Am. Surg., **172**:180, 1970.
18. Saunier, C.: Les Anomalies de la Frequency et du Rhythme Ventilatoire. Bull. Physio-Pathol. Resp., **1**:569, 1965.
19. Scrapelli E. M.: The Surfactant System of the Lung. Philadelphia, Lea and Febiger, 1968.
20. Spencer, J. L., Zikria, B. A., Kinney, J. M., Broell, J. B., and Michailoff, T. M.: A system for the Continuous Measurement of Gas Exchange and Respiratory Functions. J. Appl. Physiol., **33**:523, 1972.
21. Starr, A. and Gilman, S.: The Effect of Postoperative Intercostal Nerve Block on Pulmonary Ventilation. N. Engl. J. Med., **227**:102, 1942.
22. Williams, J. V., Tierney, D. F. and Parker, H. R.: Surface Forces in the Lung, Atelectasis and Transpulmonary Pressure. J. Appl. Physiol., **21**:819, 1966.
23. Zikria, B. A., Spencer, J. L., Michailoff, T. M., Broell, J. R. and Kinney, J. M.: Breathing Patterns in Preoperative, Postoperative and Critically Ill Patients. Surg. Forum, **22**: 40, 1971.

One-Stage Operative Therapy for Salmonella Mycotic Abdominal Aortic Aneurysm

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ABDOMINAL AORTIC ANEURYSM associated with salmonella arteritis represents a formidable surgical problem with a reported high mortality rate.[10] Surgical correction with reconstruction by placement of a vascular prosthesis within the septic field has generally been unsuccessful because of renewed sepsis in the synthetic graft placed in an infected region.[3] Presented with this problem, we performed an immediate one-step procedure combining prosthetic vascular bypass through a non-septic field with secondary, isolated resection of the infrarenal abdominal aorta which was the focus of salmonella arteritis. We utilized the principles stressed for treatment of infected aortic bifurcation grafts where the resection of the diseased aortic segment was performed in a totally anatomically separate field from the vascular bypass procedure. The report presents a patient surviving over one year following this approach to the problem.

Case Report

A 62 year–old–man presented to this hospital because of fever, anorexia, and a 40 lb. weight loss. He was in excellent health until 10 weeks prior to admission at which time he began to have recurrent episodes of fever and shaking chills with the temperature ranging up to 39.4° C. Initial physical examination demonstrated no positive physical findings except for a fever of 38.4° C. in a man who appeared chronically ill. Five out of ten blood cultures were positive for salmonella, type D. Urine and stool cultures also produced salmonella, type D. An oral cholecystogram was twice non-functioning. Chloramphenicol therapy was instituted; however, persistent high-grade bacteremias persisted. Because of the continuing septicemias in spite of antibacterial therapy a vascular source from a salmonella arteritis was suspected and a transfemoral aortogram was carried out. This demonstrated a saccular infrarenal abdominal aortic aneurysm (Figs. 1 & 2). There was slight angiographic evidence of arteriosclerotic vascular disease, and there was no evidence of vertebral erosion. The patient at this time was asymptomatic with the exception of continuing low grade fevers and had a normal abdominal examination.

The patient was prepared for surgery where a left thoracotomy and left flank incision were made for placement of a bypass graft. A 16 mm. knitted Dacron bypass graft was placed from the descending aorta to the distal left external iliac artery. This graft was placed in an extra-pleural plane, led through the diaphragm and then routed in a lateral extra-peritoneal position on the lumbar and lateral wall musculature. A 10 mm. knitted Dacron graft was then constructed from the 16 mm. graft to the right external iliac artery. This was also done extra-peritoneally via the transpubic route. After opening the grafts both external iliac arteries were temporarily occluded proximal to the anastamoses with pump tourniquets. These were led out through the incisions for later removal, and was done in order to insure continued flow through the bypass grafts. After these incisions were closed, the patient was repositioned and the abdomen reprepared as for a separate procedure.

The abdominal aorta was then exposed through a midline transperitioneal incision. There was extensive acute and chronic inflammation throughout the retroperitoneum but no gross suppuration. The abdominal aorta with a small antero-lateral aneurysm was resected from the infrarenal position to the common iliac bifurcations. The infrarenal aorta and iliac vessels were closed by two layers of running non-absorbable synthetic sutures. After closure of the retroperitoneum a cholecystectomy of a grossly normal gallbladder was carried out. The patient tolerated this procedure satisfactorily and postoperatively pedal pulses were present. The postoperative course was uncomplicated and relatively smooth. Ampicillin therapy was administered intraoperatively and postoperatively for a 6–week period. Multiple blood cultures after antibiotic therapy was terminated were negative. The pathologic specimen demonstrated a saccular and fusiform mycotic abdominal aortic aneurysm with some mild atherosclerotic plaque formation. Both the aortic wall and the retroperitoneum grew positive cultures for salmonella, type D. The gallbladder,

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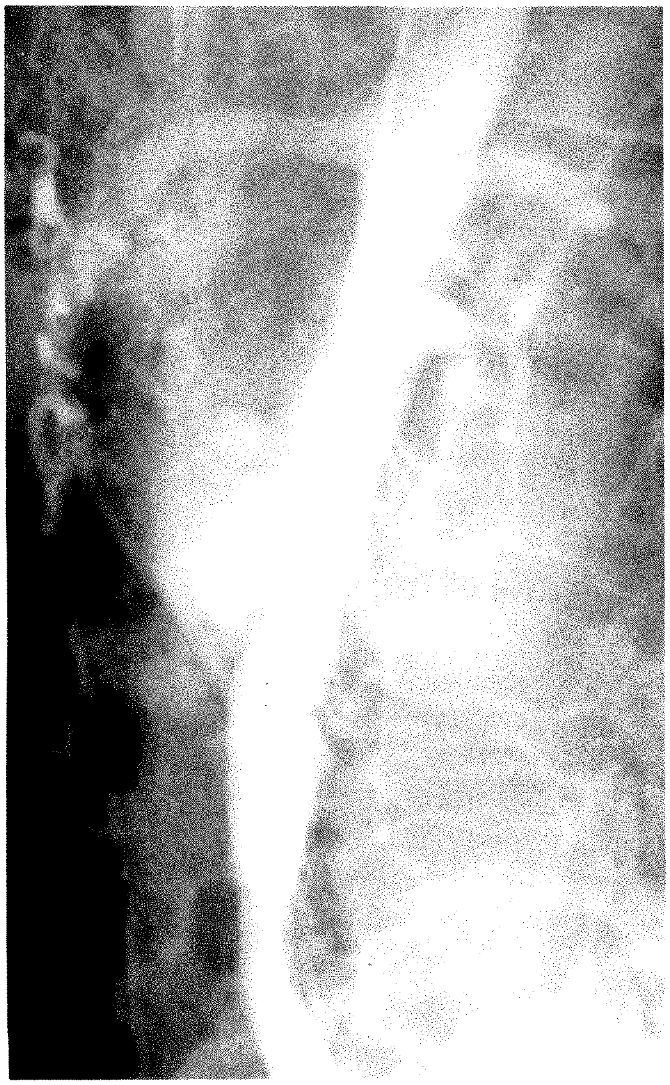

FIG. 1. Frontal projection of a transfemoral aortogram showing a saccular cryptogenic mycotic aneurysm secondary to salmonella arteritis in a 62-year-old man presenting with salmonella septicemia.

however, was sterile. Fifteen months later the patient is in excellent health and has returned to work as a taxi driver. Follow-up aortogram (Figs. 3, 4) shows that the reconstruction is in excellent condition and there are no further problems in the residual aorta.

Discussion

Aneurysms due to infection, although less common than those secondary to atherosclerosis, are still far from being rare and are amongst the oldest arterial lesions described in the Western literature. Ambrose Paré in the 16th Century originally recognized that aneurysmal disease could be secondary to syphillis. Mycotic aneurysms, on the basis of other organisms, were only recognized as an entity later. In 1853, Tufnell[16] described a peripheral aneurysm whose origin was embolic transfer from endocardial vegetations. The term "mycotic" aneurysm comes from Osler's[11] classic description of subacute bacterial endocarditis in 1885 in which infectious aneurysms are described. Goodhart,[6] in 1887 clearly described the pathogenesis and pathology of the lesion. A very early report in 1923 by Stengel and Wolferth[15] presented 217 cases of mycotic aneurysm which showed that the aorta was the most frequent site involved.

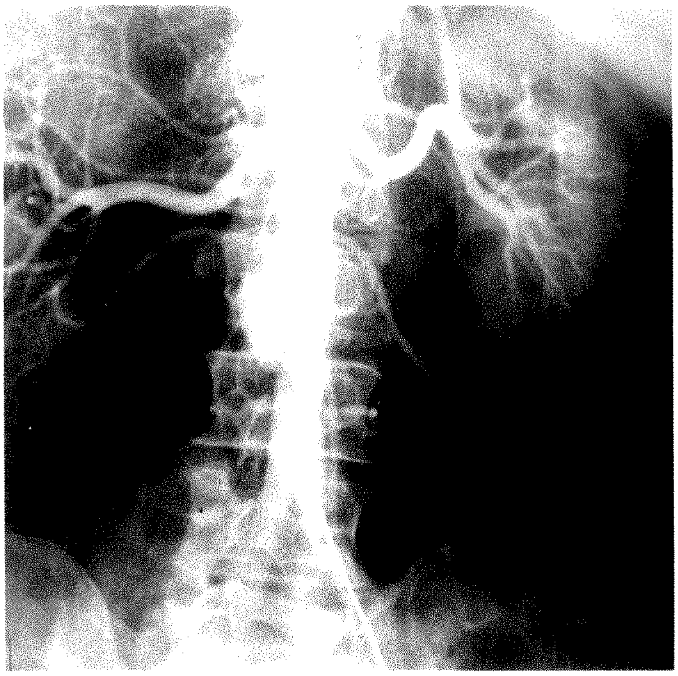

FIG. 2. Lateral projection of a transfemoral aortogram showing the same as Fig. 1, but also atherosclerotic disease in the posterior aortic wall and a slight fusiform component. No vertebral erosion is present.

The pathogenesis of mycotic aneurysms has been well and frequently described although the terminology is not completely clear.[7] However, the focus of infection may become localized in the arterial wall in 3 ways. The first mechanism is via a septic embolus within the arterial lumen usually from bacterial endocarditis. This is the most common pathogenesis occurring about 80% of the time and has been termed secondary or embolomycotic aneurysm appropriately.[8] The second mechanism is by extension from an adjacent suppurative process either directly or by way of perivascular lymphatics. The third mechanism is via lodgment of circulating viable organisms within the wall of the artery during the course of a septicemia from either an obvious or an unknown focus. Infectious arteritis occurs when organisms become established either in the vasa vasorum or in an area of underlying disease such as an ulcerated atheromatous plaque. The latter 2 pathogenic mechanisms have both been termed primary mycotic aneurysms following Crane's description in 1937.[4] This is confusing, however, and it seems better to term the last of the three, that is via bloodstream infection, cryptogenic mycotic aneurysm

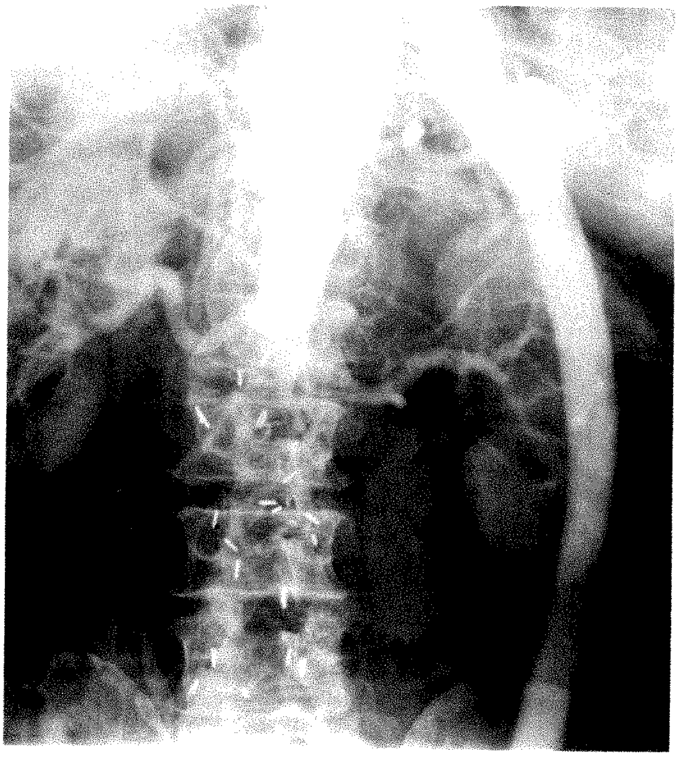

FIG. 3. Aortogram one year after one-stage therapy for mycotic aneurysm show in Figs. 1 & 2. No disease in residual aorta is seen. Note thoraco-iliac bypass through non-infected tissue planes.

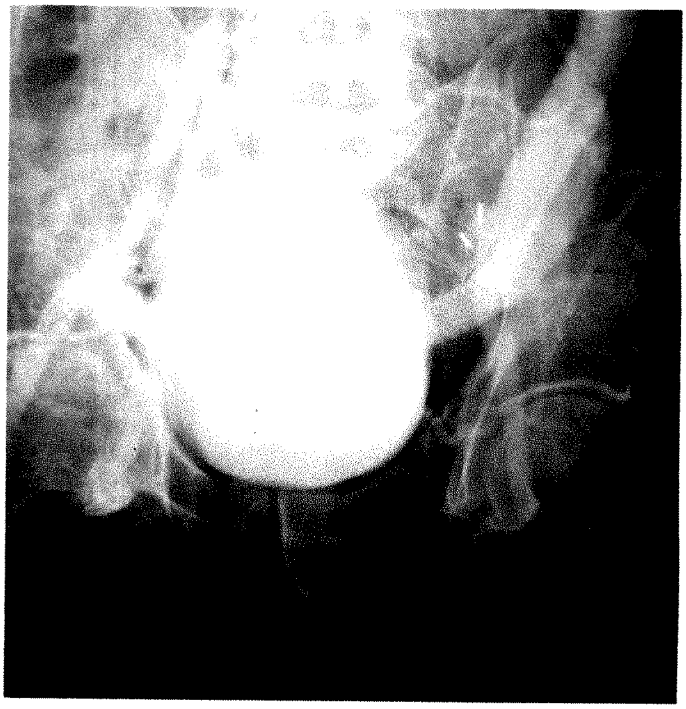

FIG. 4. Distal view of same aortogram shown in Fig. 3 .Note prosthetic bypass via transpubic route from thoraco iliac graft to right external iliac artery.

as suggested by Blum[2] since an obvious source of infection is so often inapparent. Thus, a modern, descriptive classification of mycotic aneurysms would include secondary or embolo-mycotic, primary from a localized periarterial suppurative process, and cryptogenic such as in the case presented where the source was not proven.

Once a septic process is established, changes occur in a fairly predictable fashion. Suppuration leads to destruction of the media and the weakened arterial wall subsequently yields and dilates. Eventually this will lead (sometimes rapidly and insidiously) to rupture which is a common mode of presentation and death in these patients. It is important to realize that once the aneurysm has become established, no matter what its source, that antimicrobial therapy will not be effective in preventing complications and further progression. In addition, the micro-organisms present in all mycotic aneurysms will continue to be seeded into the blood stream with continued intermittent septicemias such as seen in the case presented.

The etiologic organism causing mycotic aneurysm can be virtually any which are recognized as causing clinical infection including tubercle bacilli and fungi although those most commonly seen are streptococci, staphylococci, pneumococci, and salmonella. Salmonella is a fairly common organism found especially in the cryptogenic aneurysms or arteritides since it is thought that salmonella has a particular predilection for diseased arterial walls leading to about 35% of all such mycotic aneurysms.[11] Other frequent primary foci for salmonella organisms are the gastro-intestinal and biliary tracts. Since salmonella infection is relatively easy to eradicate in these latter 2 locations, it becomes important to recognize that in patients such as the one described, that recurring salmonella septicemias in the presence of adequate antimicrobial therapy should alert the clinician to an intra-arterial source.

Mycotic aneurysms and especially those due to salmonella are among the most difficult arterial lesions to treat. The general principles of management of mycotic aneurysms have been elaborated by Mundth, *et al.*[10] and by Fromm.[5] They are similar to the principles in managing infection complicating vascular reconstructive surgery.[13] Two main concepts have been established. First, the septic field including the aneurysm must be resected. Second, the placement of the prosthetic bypass graft must eventually be through a clean, non-septic tissue plane. Salvage in these difficult situations can only be achieved by application of these concepts but even in these instances success is not uniformly achieved. Mortality associated with salmonella infection in abdominal aortic aneurysm seems to be particularly high. In fact, the 4 patients in Mundth's series with salmonella infection failed to survive.[1] Reichle,[12] and Sower,[14] emphasized these principles in their successful management of 2 of the only 3 reported survivors from mycotic abdominal aortic aneurysm secondary to salmonella arteritis. In these cases, however, the surgical approach was different in that staged procedures were utilized. First, temporary bifurcation grafts were placed following resection of the mycotic aneurysm. This, alone, has been shown to result in complicating sepsis and ultimate failure as mentioned earlier.[2] Therefore, secondly they proceded to resect the temporary graft and place a bypass through clean tissue planes. This resulted in survival.

The fact that survival can also be accomplished with a one-stage procedure incorporating these principles is the purpose of this case presentation. Presented with an unruptured cryptogenic mycotic abdominal aortic aneurysm, vascular bypass through clean tissue planes was carried out followed by resection of the aneurysm through a separate operative field which constituted a definitive solution for the problem. An intensive effort to control the blood stream infection was made before the operative stage and then a prolonged course of antimicrobial therapy was given postoperatively. Application of all these features can be credited towards the successful long term outcome in the patient presented which is the fourth reported survivor of salmonella mycotic abdominal aortic aneurysm. Although a survivor was reported by Meade[9] in which the reconstructing aortic graft was placed within the septic field, it is strongly felt that to gain the highest successful yield in this difficult problem, a one-stage procedure leading to a low risk of subsequent sepsis, should be employed.

Summary

Abdominal aortic aneurysm from salmonella arteritis is an uncommon but difficult surgical problem. Successful management of a patient with such a lesion is presented which is only the fourth reported survivor. Application of the principles of resection of the infected vessel plus reconstruction through non-infected tissue planes were carried out as a single one-stage procedure. Careful adherence to these principles are credited with an excellent long term outcome.

References

1. Bennett, D. E., and Cherry, J. R. Bacterial Infection of Aortic Aneurysms. Amer. J. Surg. **113**:321, 1967.
2. Blum, L., & Keefer, E. B. C. Cryptogenic Mycotic Aneurysm. Annals of Surg. **155**:398, 1962.
3. Cliff, M. M., Soulen, R. L., and Finestone, A. J.: Mycotic Aneurysms—A Challenge and a Clue. Arch. of Intern. Med. **126**:977, 1970.
4. Crane, A. R. Primary Multilocular Mycotic Aneurysms of the Aorta. Arch. Path. **24**:634, 1937.
5. Fromm, S. H., and Lucas, C. E.: Obturator Bypass for Mycotic Aneurysm in the Drug Addict. Arch. Surg. **100**:82, 1970.
6. Goodhart, J. F.: Cases of Aneurysm from Embolism. Tr. Path Soc. London **28**:106, 1887.
7. Karsner, H. T.: *Acute Inflammation of Arteries*. p. 16 Chas. C. Thomas, Springfield, Illinois, 1947.
8. Labardini, M. M., and Dow, R. W.: Primary Mycotic Aneurysms of the Right Common Iliac Artery. Arch. Surg. **96**:373, 1968.
9. Meade, R. H., and Moran, J. M.: Salmonella Arteritis: Preoperative Diagnosis and Cure of Salmonella Typhimurium Aortic Aneurysm. New Eng. J. Med. **281**:310, 1969.
10. Mundth, E. D., Darling, R. C., Alvarado, R. H., Buckley, M. J., Linton, R. R., and Austen, W. G.: Surgical Management of Mycotic Aneurysms and the Complications of Infection in Vascular Reconstructive Surgery. Amer. J. Surg. **117**:460, 1969.
11. Osler, W.: On Malignant Endocarditis. Brit. Med. J. **1**:467, 1885.
12. Reichle, F. A., and Tyson, R., Soloff, L., Lautsch, E., and Rosemond, G. Salmonellisis and Aneurysm of the Distal Abdominal Aorta. Annals of Surg. **171**:219, 1970.
13. Shaw, R. S., and Baue, A. E.: Management of Sepsis Complicating Arterial Reconstructive Surgery. Surg. **53**:75, 1963.
14. Sower, N. D., and Whalen, T. J.: Suppurative Arteritis Due to Salmonella. Surg. **52**:851, 1962.
15. Stengel, A., and Wolferth, C. C.: Mycotic (Bacterial) Aneurysms of Vascular Origin. Arch. Intern. Med. 31:527, 1923.
16. Tufnell, J.: On the Influence of Vegetation of the Valves of the Heart in the Production of Secondary Arterial Disease. Dublin Quart. J. Med. Sci. **15**:371, 1853.

Effect of Partial and Total Vagotomy on the Gastric Acid Response to an Insulin Infusion in the Dog

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THE GASTRIC ACID RESPONSE to insulin hypoglycaemia has been found to be unaffected by division of 50% or even as much as 75% of the vagal fibres at the hiatus in the dog.[5,9] Such findings would support the concept that the effect of vagotomy on gastric secretion is an "all-or-none" phenomenon but would appear incompatible with the notion that, below the oesophageal plexus, canine gastric vagal innervation is segmental.[4,6] Recently, however, insulin induced acid secretion was reportedly reduced by 35% to 50% after transthoracic hemivagotomy.[10]

In these experiments, started 3 to 4 weeks following partial vagotomy, acid secretion was induced by a single rapid intravenous injection of insulin which provides a transient hypoglycaemic stimulus. In contrast, an insulin infusion provides in dogs with intact vagi a steady glycopenic stimulus by producing a prolonged plateau of hypoglycemia.[3]

The present study was designed to investigate, 3 to 6 months after the vagotomy operation, the effect of total and partial vagotomy on gastric acid secretion induced by a continuous infusion of insulin and, in the event that partial vagotomy would reduce acid secretion, to ascertain whether a dose-response relationship exists in partially vagotomized dogs.

Methods

A chronic gastric fistula was established in each of 4 mongrel male dogs (weight 10 to 14 kg) using a Thomas cannula,[12] placed just proximal to the pyloric gland area. A 3 week recovery period was allowed before initiating the gastric secretory studies. Each dog was fasted for 20 hours before each test. Two 15-minute samples of basal gastric secretion were collected before the insulin infusion was started. Soluble insulin (Insulin B.P., Burroughs Wellcome) in doses of 0.025, 0.05, 0.15 and 0.30 units per kg of body weight per hour, was diluted in 154 mM NaCl and delivered intravenously for 3 hours, using a constant slow injection pump (C.F. Palmer, London). Samples of gastric juice were collected every 15 minutes and each measured for volume (ml/15 min), acid concentration (mEq/L) and acid output mEq/15 min). All titrations were made to pH 7.0 with 0.01 N NaOH, using an EIL Titrimeter (Electronic Instruments Limited, Richmond, Surrey, England). Samples of venous blood were also obtained just prior to and every 30 minutes after the start of the infusion and blood glucose levels determined by a glucose oxidase method using an Autoanalyser.

Each dose was given 3 times to each dog and the order of administration of insulin dose was randomized. No animal was tested more often than every other day.

After completion of the initial studies in the non vagotomised dogs, a transthoracic vagotomy was performed through a left thoracotomy. In each instance, two major vagal trunks, one anterior and one posterior, were identified at the hiatus and just proximal to it. In 2 dogs (A and B) all vagal fibres were divided, while in the other two dogs (C and D), only the anterior trunk was divided. In both types of vagotomy, a nerve segment of three centimetres was excised.

Following vagotomy, a 3 month recovery period was allowed before repeating the tests which were carried out over a period of three months.

Terminology

The following parameters of acid secretion were measured:

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1) the peak 15-minute acid output (PAO$_{15}$), being the highest 15-minute collection during the infusion, expressed as mEq/15 min;

2) the peak 30-minute acid putput (PAO$_{30}$), calculated as the sum of the two highest consecutive 15-minute collections during the infusion, expressed as mEq/30 min;

3) the plateau acid putput (P$_L$AO), calculated as the sum of the four highest consecutive 15-minute outputs during the infusion and expressed as mEq/hr^2; and

4) the total acid output (TAO), calculated as the sum of all twelve 15-minute samples during the infusion and expressed as mEq/3 hours.

Results

The mean acid response to the insulin infusion is shown in Figs 1–3. The outputs of acid in dogs A and B (Fig. 1) are presented as the overall mean (mean of means) since they were of the same magnitude. In these 2 dogs, the peak and total acid outputs increased significantly ($p < 0.05$) with increasing doses of insulin, up to 0.15 u/kg/hr. Total vagotomy completely abolished the acid response to insulin hypoglycaemia.

Partial vagotomy, however, repeatedly reduced the acid response to insulin in dogs C and D (Fig. 2 and 3 and Table 1). The PAO$_{15}$, PAO$_{30}$, P$_L$AO and TAO (see terminology) increased significantly ($p < 0.05$ to <0.001) with increasing doses of insulin, up to 0.15 u/kg/hr, both before and following vagotomy. In both dogs, the acid outputs in response to 0.30 u/kg/hr of insulin tended to be less than that obtained with 0.15 u/kg/hr, but this did not always achieve statistical significance.

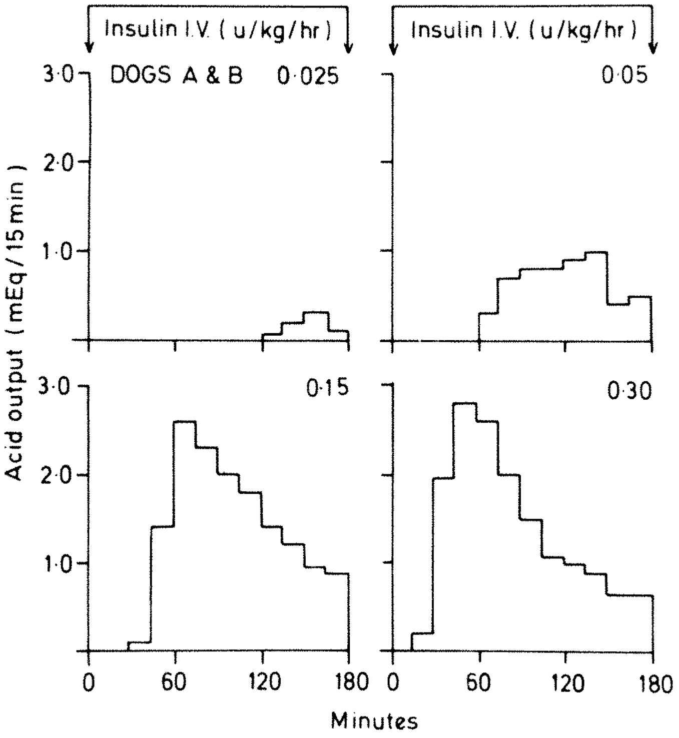

FIG. 1. Acid response to insulin infusion in dogs with intact vagal innervation. Each value represents the overall mean (mean of means) of 3 tests.

The timing of the peak acid responses was not consistently altered by partial vagotomy.

Basal acid outputs have not been included in Figs. 1–3 since they were extremely low (<0.2 mEq) or virtually absent in dogs A and B before vagotomy. It was therefore impossible to detect any change following vagotomy.

The reduced acid response observed following partial vagotomy was expressed as a percentage of the prevagotomy acid response (Table 1). The degree of reduction of the acid response decreased significantly ($p < 0.001$) with increasing doses of insulin up to 0.15 u/kg/hr. The reduction observed with 0.30 units was significantly ($p < 0.001$) greater than that seen with 0.15 u/kg/hr of insulin.

Blood glucose values (Fig. 6) were nearly identical before and following vagotomy.

Discussion

Total vagotomy completely abolished, while partial vagotomy significantly reduced below prevagotomy levels the acid response to insulin hypoglycaemia. Our results indicate that the stomach does not respond in an "all-or-none" fashion to vagal stimulation.

Similar findings have been obtained in partially vagotomised dogs,[10] cats,[10] ferrets[1] and rats,[7] when a single injection of insulin was used to stimulate gastric secretion. Our experiments, in which an infusion of insulin was employed, confirm these earlier findings and support the notion of a segmental vagal innervation of the parietal cell mass below the oesophageal plexus in the dog.

In contrast, Legros and Griffith[5] did not observe any reduction in the insulin induced acid secretion after either anterior or posterior vagotomy in the dog. They explained that with incomplete vagotomy due to an intact vagal trunk, secretion from the residually innervated gastric wall remains unchanged, while the vagally denervated wall will secrete acid in response to vagally released gastrin from the antrum.[6] Circulating gastrin was not measured during our experiments, but even if gastrin was released in increased amounts, it could not compensate for the complete vagal denervation of half of the stomach. Similarly, Sebus and Charbon,[9] recovering gastric juice by way of a nasogastric tube from their dogs, were unable to detect any change in the insulin induced acid response following a 75% vagal denervation of the stomach. Poor recovery of the gastric content might possibly explain their results. Clearly, in our experi-

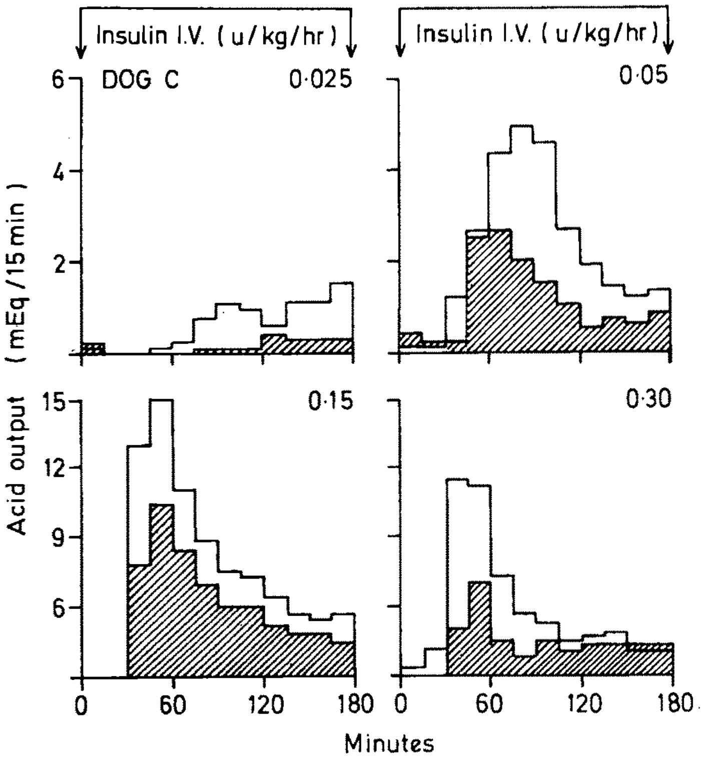

FIG. 2.

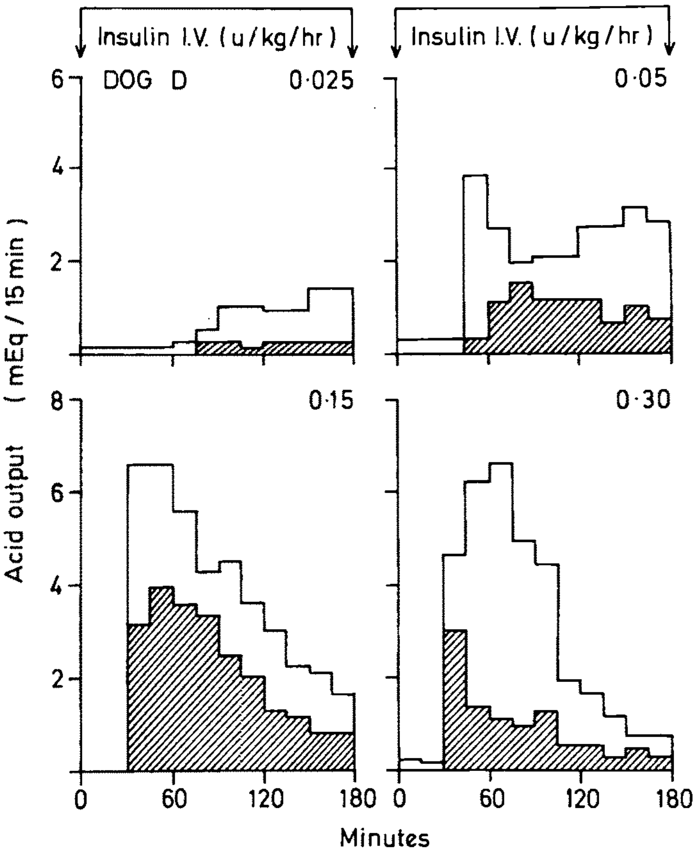

FIG. 3.

FIG. 2 and 3. Mean acid response (mean of 3 tests at each dose) to insulin infusion before (clear area) and following (shaded area) partial vagotomy.

ments in dogs, partial vagotomy significantly lowered the acid response to insulin. This difference did not depend on blood glucose changes since prevagotomy and postvagotomy hypoglycaemic levels were nearly identical.

All previously mentioned investigators began their gastric secretory studies 3 or 4 weeks following partial vagotomy.[1,5,7,9,10] Our tests were purposely commenced at least 3 months following the operation, so that any change in the acid response could not be attributed to a temporary post-operative reduced capacity of the stomach to secrete acid. It has recently been shown in men submitted to serial insulin tests in the first year follow-

TABLE 1. *Acid Response Before and After Partial Vagotomy*

		Insulin Infusion (u/kg/hr)											
		0.025			0.05			0.15			0.30		
Acid Output	Dog	Pre vag	Post vag	% Red	Pre vag	Post vag	% Red	Pre vag	Post vag	% Red	Pre vag	Post vag	% Red
PAO_{15}*	C	1.97	0.50	73	5.92	3.26	45	12.2	7.48	39	8.61	3.92	54
	D	1.53	0.37	75	3.86	1.52	60	7.14	4.17	41	6.60	3.02	54
PAO_{30}*	C	3.53	0.92	70	10.4	5.32	48	22.2	14.2	37	16.9	5.89	64
	D	2.78	0.68	72	6.58	2.74	58	13.4	7.84	41	12.8	4.28	66
P_LAO*	C	5.44	1.71	66	17.6	9.20	48	35.3	22.2	37	24.2	8.02	66
	D	4.58	1.09	79	11.3	4.95	52	23.4	13.9	40	22.2	6.23	70
TAO*	C	8.03	2.38	70	26.2	13.5	48	55.3	35.9	35	34.3	13.0	62
	D	7.67	1.60	79	24.7	10.3	58	40.8	23.3	42	32.6	9.58	70
Mean % Reduction (± S.E.M)		73 ± 1.6			52.6 ± 2.1			39 ± 0.67			63.2 ± 2.2		

Overall % reduction: 57%
* See text.

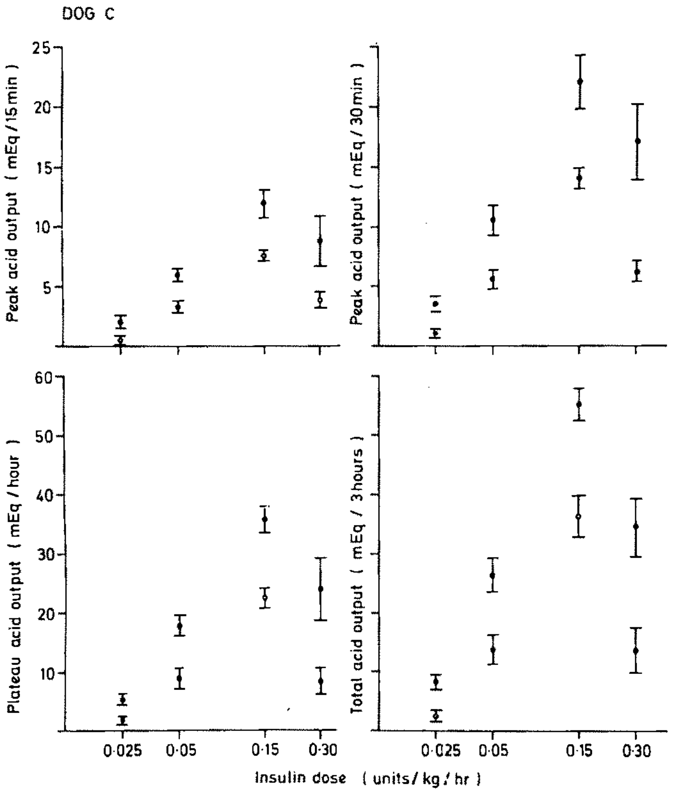

FIG. 4.

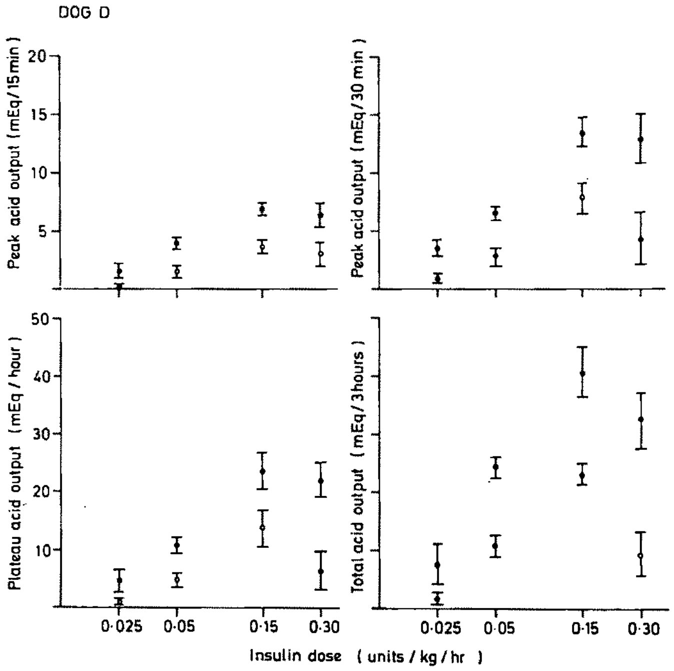

FIG. 5.

FIG. 4 and 5. The PAO_{15}, PAO_{30}, P_LAO and the TAO (see text) increased significantly, ($0.05 > p < 0.001$, Student's t-test for unpaired data) with increasing doses of insulin (up to 0.15 u/kg/hr) before (closed circles) and after (open circles) partial vagotomy. The acid outputs after vagotomy were significantly ($p < 0.05$ to < 0.001) reduced with all doses of insulin. Each circle represents mean of 3 tests (±S.E.M.). Insulin dose represented on logarithmic scale.

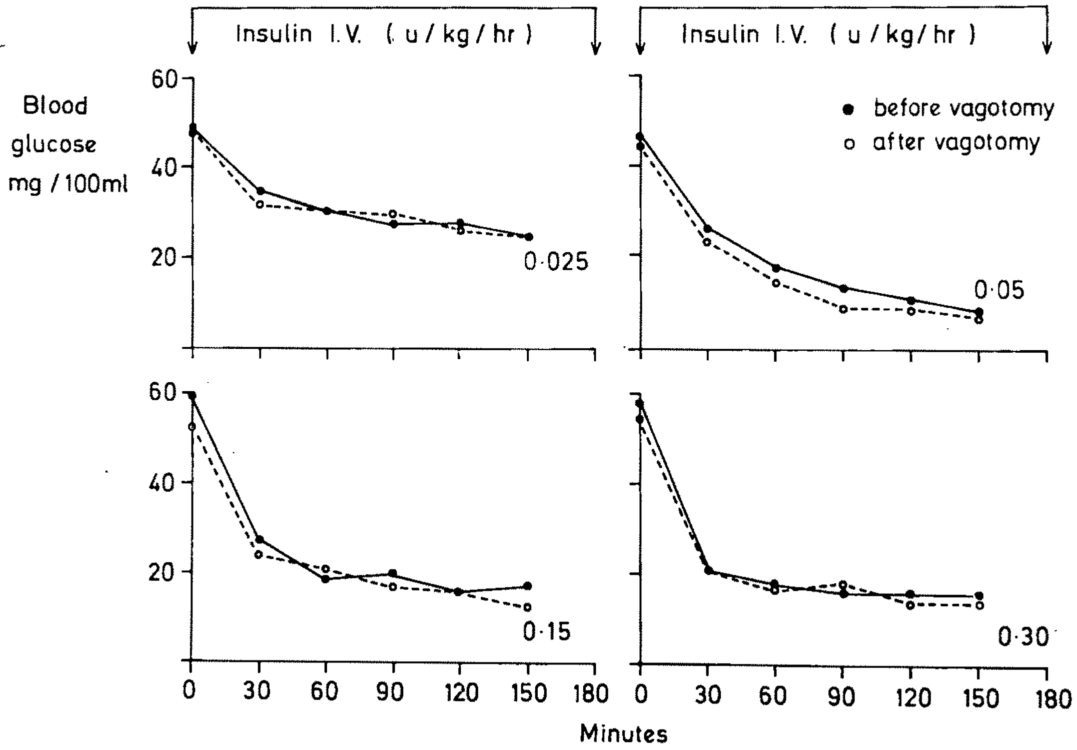

FIG. 6. Blood glucose values in response to graded doses of insulin before (closed circles) and after (open circles) vagotomy. Each value represents the overall mean (mean of means of 3 tests) in 4 dogs.

ing vagotomy that conversion of the insulin acid response occurs primarily within 6 months following the operation and is associated with a significant increase in the acid output.[8] Repetition of the tests at one year in our animals would establish the long term stability of the acid response to insulin after partial vagotomy.

A quantitative relationship between insulin dose and acid response was observed both before and after partial vagotomy. Partial vagotomy reduced the acid response to all doses of insulin, but did not change the amount of insulin necessary to produce the decreased maximal acid response. Similar findings were obtained by Stening and Grossman.[11] The mean acid reduction in partially vagotomised dogs ranged between 39 and 73% and was dose-related in that more important degrees of reduction were observed with doses of insulin producing submaximal acid responses. Since anterior vagotomy denervates completely (100%) half of the stomach,[11] one would expect a 50% reduction in the acid response to insulin. Changes in circulating gastrin levels after partial vagotomy and graded doses of insulin might explain our findings but further work is needed.

Summary

Total vagotomy completely abolished, while partial vagotomy significantly reduced (57%) the acid response to an insulin infusion in the dog. The reduced acid response after partial vagotomy was noted to be graded with doses of insulin producing submaximal acid responses.

These findings indicate that the stomach does not respond in an "all-or-none" fashion to vagal stimulation and support the notion of a segmental innervation of the parietal cell mass below the oesophageal plexus.

Acknowledgments

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References

1. Basso, N., Umeda, N., Roth, J. L. A., Passaro, E. and Pfeiffer, C. J.: Effect of Unilateral Vagotomy on Gastric Secretion in the Ferret. Gastroenterology, **61**:207, 1971.
2. Carter, D. C., Dozois, R. R. and Kirkpatrick, J. R.: An Insulin Infusion Test of Gastric Acid Secretion. Brit. Med. J. **2**: 202, 1972.
3. Dozois, R. R., Carter D. C. and Kirkpatrick, J. R.: Gastric Secretory Response to Continuous Insulin Infusion in the Dog. (Abstract). Brit. J. Surg. **60**:311, 1973.
4. Jemerin, E. E., Hollander, F. and Weinstein, V. A.: A Comparison of Insulin and Food for the Differentiation of Vagal and Non Vagal Gastric Pouches. Gastroenterology, **1**:500, 1943.
5. Legros, G. and Griffith, C. A.: The Anatomic Basis for the Variable Adequacy of Incomplete Vagotomy. Ann. Surg. **168**:1035, 1968.
6. Pritchard, G. R., Griffith, C. A. and Harkins, H. N.: A Physiologic Demonstration of the Anatomic Distribution of the Vagal System to the Stomach. Surg. Gyn. and Obst., **126**: 791, 1968.
7. Rivilis, J., Yaffe, M. and Preshaw, R. M.: The Effect of Unilateral Vagotomy on Gastric Secretion in the Pylorus Ligated Rat. Proc. Soc. Exp. Biol. Med. **127**:310, 1968.
8. Smith, I. S., Gillespie, G., Elder, S. B., Gillespie, I. E. and Kay, A. W.: Time of Conversion of Insulin Response after Vagotomy. Gastroenterology, **62**:912, 1972.
9. Sebus, J. and Charbon, G. A.: Partial Vagotomy and Gastric Secretion in Dogs. Gastroenterology, **44**:311, 1963.
10. Stening, G. F. and Isenberg, J. I.: Insulin Induced Acid Secretion After Partial Vagotomy in Dogs and Cats. Amer. J. Physiol., **217**:962, 1969.
11. Stening, G. F. and Grossman, M. I.: Effect of Partial Vagotomy in the Neck and Lower Thorax on Insulin Stimulated Acid Secretion in Dogs. Gastroenterology, **59**:376, 1970.
12. Thomas, S. E.: An Improved Cannula for Gastric and Intestinal Fistulas. Proc. Soc. Exp. Biol. Med. **46**:260, 1941.

Current Status of Bilateral Adrenalectomy or Advanced Prostatic Carcinoma

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THE INITIAL REDUCTION of androgenic hormone by bilateral orchiectomy and/or estrogen therapy may produce a regression of advanced prostatic carcinoma.[6] Measurement of the 24-hour secretion of urinary 17-ketosteroids in castrated patients correlates well with relapse of the disease,[15] and can be decreased again after bilateral adrenalectomy.[4,7] Since cortisone has become available, adrenalectomy has been used to a limited extent following relapse of advanced carcinoma of the prostate. Previous investigators have agreed that bilateral adrenalectomy produced a remarkable degree of subjective improvement (Table 1), but it has been unclear as to whether increased survival with objective responses could be satisfactorily obtained.

Bilateral adrenalectomy for disseminated prostatic carcinoma had been performed in Roswell Park Memorial Institute since October 1969 and some of the short term follow-up results have been discussed previously.[13,16] This report presents current clinical results and other important biological correlates in a longer term of follow-up for our series.

Materials and Methods

Twenty-six patients with proven disseminated and reactivated prostatic carcinoma were selected for bilateral adrenalectomy since October, 1969. The present period of follow-up evaluation was extended until April, 1972. Sixteen of these patients had relapsed from previous castration and estrogen treatment for periods of time varying from 6 months to 134 months (Fig. 1, Cases 1–14, 19, 20). Five patients had orchiectomy within a prior period of 2–4 months and had no relapse at the time of adrenalectomy (Fig. 1, Cases 15–18, 21). The last 5 patients (Fig. 1, Cases 22–26) had relapsed from previous castration followed by hypophysectomy.

The ages of the patients at the time of adrenalectomy ranged from 53 years to 74 years, the mean age being 65. All patients at the time of adrenalectomy presented major symptoms of back and hip pain. Four patients (Fig. 1, Cases 11, 13, 17, 18), had no definite bone metastases but 3 of these had soft tissue metastases (Fig. 1, Cases 11, 13, 18), and 1 patient (Fig. 1, Case 17) had mainly severe back pain with marked elevation of serum acid phosphatase. No elevation of serum acid phosphatase at the time of adrenalectomy was noted in 11 patients (Fig. 1, Cases 1, 2, 5, 7, 11, 15, 16, 18, 20, 23, 26). Two patients with ureteral obstruction (Fig. 1, Cases 1, 2), required urinary diversion at the time of adrenalectomy.

Every patient had a one-stage adrenalectomy through bilateral lumbar incisions with twelfth or eleventh rib resection. Cortisone management has been used similar to the new schedule of Morales *et al.*,[9] *i.e.* cortisone acetate 50–75 mg. per day orally, for maintenance. The dose was determined by the sense of well-being of the patient.

Postoperatively serum acid and alkaline phosphatase as well as plasma testosterone and 24-hour urinary ketosteroid excretion were studied. The patients were followed at variable periods postoperatively depending upon their clinical condition. At each follow-up chest and skeletal radiological survey, physical examination, and urine and blood studies were completed.

The criteria utilized for clinical response to this treatment were the same as that previously described.[10] Improvement of pain and sense of well-being were the main parameters of subjective improvement. A decrease of

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TABLE 1. *Results of Bilateral Adrenalectomy for Advanced Prostatic Carcinoma from a Review from Literatures*

Author	Number of Patients	Subjective Improvement* Good	Subjective Improvement* Fair	Objective Improvement**	Immediate Postoperative Death	Longest Survival
Huggins & Scott (1945)[7]	4	1	2		3	115 days
Huggins *et al.* (1952)[5]	7	3	2		1	?
Baker (1953)[1]	10	7	1			6 months
Scardino *et al.* (1953)[14]	3	1	1	1		9 months
Taylor *et al.* (1953)[17]	6	5		1		7 months
Whitmore *et al.* (1954)[18]	17	6	5	2	1	330 days
Fergusson (1954)[2]	17	9	3		2	10 months
Pyrah (1954)[12]	3	2				—
Morales *et al.* (1955)[9]	20***	4/10	5/10	1	2	24 months
MacFarlane *et al.* (1960)[8]	13	9		1		46 months (mean 13 months)

* Judged according to pain and sense of well-being.
** Judged according to growth regression (no bone improvement).
*** Only 10 patients had pain before adrenalectomy.

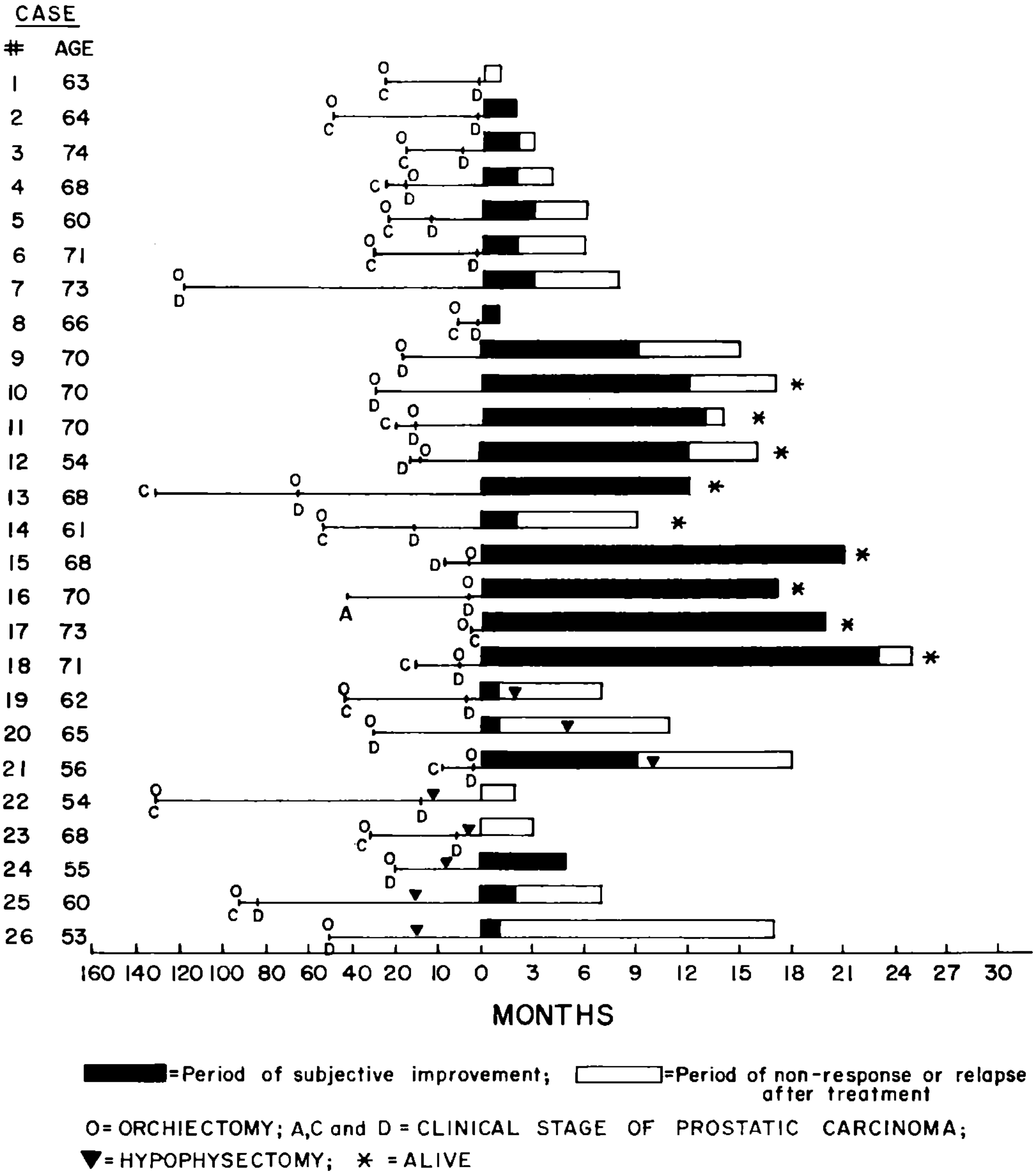


FIG. 1. The survival and remission rates for the R.P.M.I. adrenalectomy series.

TABLE 2. *Subjective Improvement After Bilateral Adrenalectomy in Disseminated Prostatic Carcinoma*

Conditions of Patient at the time of Bilateral adrenalectomy	N	Patients still Alive	Period of Subjective Improvement*			Mean Period of Subjective Improvement	Mean Survival Time**
			Up to 3M.	>3 to 12 M.	>12 M.		
Previous Castration with Relapse	16	5 cases	10 cases (62.5%)	1 case	4 cases (25%)	4.8 months	8.2 months
No relapse***	5	4 cases	—	1 case	4 cases (80%)	18.0 months	20.8 months
Previous castration and hypophysectomy with relapse	5	—	2 cases (40%)	1 case	—	1.6 months	6.8 months

N = Number of patients who had bilateral adrenalectomy.

* Period of subjective improvement after adrenalectomy in months.

** Mean survival time in months after adrenalectomy.

*** Castration 2–4 months before adrenalectomy.

serum acid phosphatase, or improvement of radiographic bone metastasis were the chief parameters of objective improvement.

Survival of patients with disseminated prostatic carcinoma treated with bilateral adrenalectomy in the present series were compared with 44 patients at the same stage of disease with clinical remission after orchiectomy and estrogen therapy at this institution.

Results

Subjective Improvement

The time course of the disease and the period of subjective improvement of the patients are summarized in Fig. 1. It shows that the majority of the patients who had a short period of subjective response (not more than 3 months) had died within 9 months. The group of patients who had a long period of subjective response (more than 9 months) had a long survival and 9 of them are still alive. These 9 patients have, to date, a mean survival time of 16.8 months, and a mean period of subjective improvement of 14.6 months. In contrast, 17 patients died with a short mean survival time of 6.8 months and a mean period of subjective improvement of 2.5 months. This difference is statistically significant ($p < 0.001$).

Table 2 shows that bilateral adrenalectomy in the patients who had relapsed after previous castration or previous castration and hypophysectomy, had a shorter mean survival time and a shorter mean period of subjec-

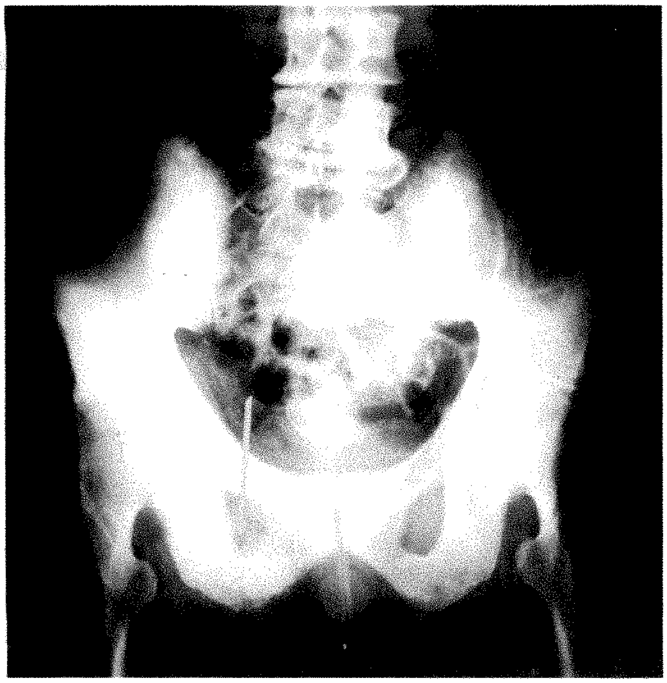


FIG. 2. Pelvic-bone x-ray of the patient (Case 15) before adrenalectomy. Note the irregularity of the border of right pubic bone (Osteoblastic lesion).

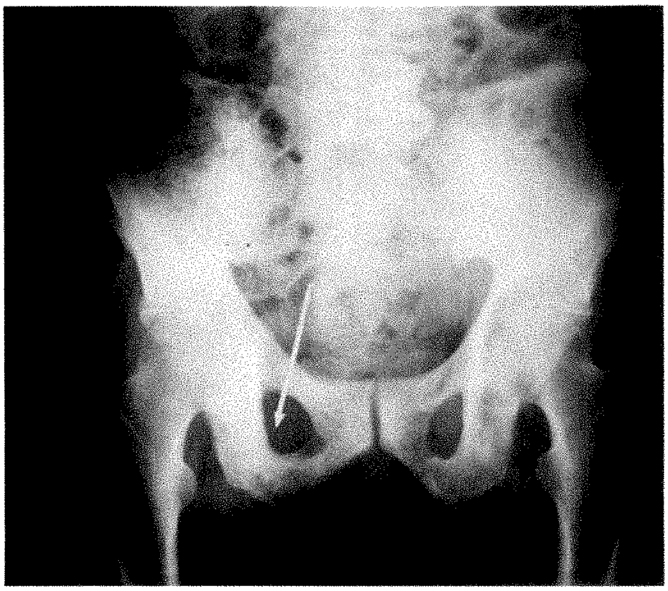
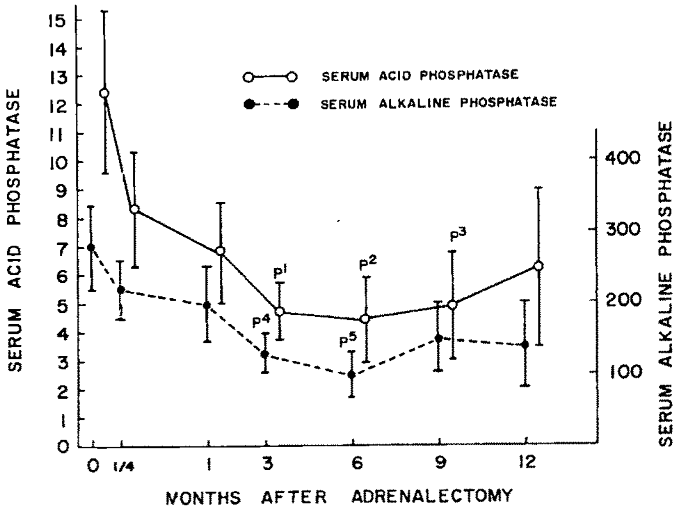


FIG. 3. Pelvic bone x-ray same patient in Case 15, 19 months after adrenalectomy. Note the sharp border of right public bone due to improvement of osteoblastic lesion.



STATISTICS: $P^1 < 0.05$, $P^2 < 0.025$, $P^3 < 0.05$, $P^4 < 0.05$, $P^5 < 0.025$

*MEAN VALUE ± S.E.M.

FIG. 4. Serum acid phosphatase levels are expressed in Babson-Read units per mililiter, with normal range of 0.5 to 4.0 units. Serum alkaline phosphatase are expressed in International units per mililiter, with normal range of 30–80 units.

tive improvement than the patients who had not relapsed from a previous short period of castration.

Objective Improvement

One patient (Fig. 1, Case 15) found partial improvement of osseous metastases as judged from radiological study (Figs. 2 and 3). Four patients who had no definite bone metastases at the time of adrenalectomy exhibited no progression of disease at the time of this study (Fig. 1, Cases 11, 13, 17, 18).

Serum acid phosphatase levels decreased 1 month after adrenalectomy in 13 of 15 patients who had preoperative elevations and increased again when these patients exhibited clinical relapse. Four patients (Fig. 1, Cases 11, 15, 16, 18) still show serum acid phosphatase values within normal limits similar to the values noted before adrenalectomy.

Fig. 4 demonstrates that the mean serum acid phosphatase in previously castrated patients shows a significant decrease after adrenalectomy: at 3 months ($p < 0.05$), at 6 months ($p < 0.025$), and at 9 months ($p < 0.05$). Mean serum alkaline phosphatase levels fell at 3 months postoperatively ($p < 0.05$) and at 6 months postoperatively ($p < 0.025$). In contrast, no significant decrease of mean serum acid or alkaline phosphatase in previously castrated-hypophysectomized patients (Fig. 5) was noted.

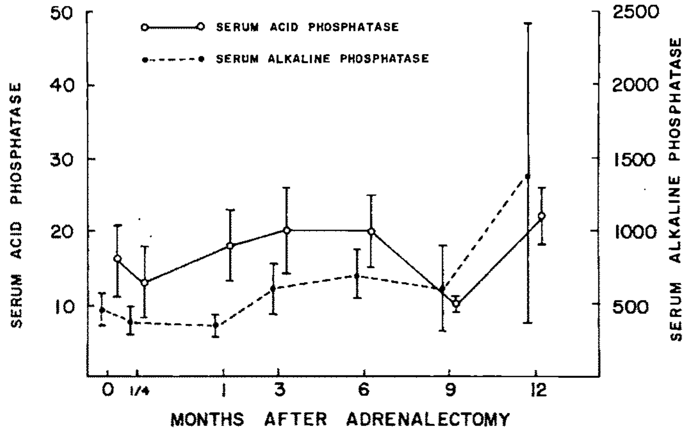


FIG. 5. Serum acid phosphatase levels are expressed in Babson-Read units per mililiter, with normal range of 0.5 to 4.0 units. Serum alkaline phosphatase are expressed in International units per mililiter, with normal range of 30–80 units.

The mean plasma testosterone value after adrenalectomy exhibited no significant change (Table 3) when followed for a 6 month period ($p > 0.05$). Twenty-four hour urinary excretion of total 17-ketosteroids in previously castrated or previously castrated-hypophysectomized patients were higher than before adrenalectomy ($p > 0.05$) (Tables 4 and 5). A marked decrease of 11-deoxy-17-ketosteroids was noted in previously castrated patients ($p > 0.05$), but no consistent change in 11-deoxy-17-ketosteroid excretion in previously castrated-hypophysectomized patients was observed. There was a significant increase of 11-oxy-17-ketosteroids after adrenalectomy in previously castrated patients (Table 4) at 2 weeks ($p < 0.01$) and at 3 months ($p < 0.05$). Fig. 6 shows that the one year survival of patients after adrenalectomy in previously castrated (pituitary intact) was 53% compared with 70% of the patients in the same

TABLE 3. *Mean Plasma Testosterone After Bilateral Adrenalectomy in Advanced Prostatic Carcinoma Patients*

(*Mean Value* ± *S.E.M.*)

		After Adrenalectomy		
	Before Adrenalectomy	1 Month	3 Months	6 Months
Previous-Castrated State	72.4 (10.7)	66.5 (18.5)	108.2 (22.5)	75.8 (12.7)
N	11	13	9	3
Previous-Castrated-Hypophysectomized State	72.8 (27.2)	37.0 (10.4)	24.0 (16.0)	19.0 (12.1)
N	5	4	2	3

N = Number of patients.
Normal range is 400–1200 ng per 100 ml

TABLE 4. *Twenty-four Hour Urinary Ketosteroid Excretion[3] After Bilateral Adrenalectomy in Advanced Prostatic Carcinoma Patients with Prior Castration (Mean Value ± S.E.M.)*

	Before Adrenalectomy	After Adrenalectomy 2 Weeks	After Adrenalectomy 1 Month	After Adrenalectomy 2–3 Months
Total 11-Deoxy-17-Ketosteroids	2.56 (0.60)	1.30 (0.17)	1.59 (0.34)	1.32 (0 54)
N	15	17	7	8
Total 11-Oxy-17-Ketosteroids	1.48 (0.30)	4.39 (0.95)*	4.97 (1.66)	4.27 (1 22)**
N	15	17	7	8
Total 17-Ketosteroids	4.04 (0.71)	5.66 (0.97)	6.61 (1.8)	5.60 (1.72)
N	15	17	7	8

N = Number of Patients
* $p < 0.01$
** $p < 0.05$

stage of the disease who had been treated by orchiectomy and estrogen and were still alive after a period of three years.

Fig. 7 shows that the patients who were treated by bilateral adrenalectomy in previously castrated (without pituitary) had a 1 year survival of 25% compared to 72% of the same stage of patients who were treated by orchiectomy and estrogen and were still alive after a period of 4 years.

Causes of Death

Causes of death are tabulated in Table 6. Regardless of prior castration or castration plus hypophysectomy, most patients died as a result of their primary disease.

Discussion

At the present time, endocrine therapy for advanced prostatic carcinoma remains palliative. The majority of reported patients have exhibited remarkable responses to orchiectomy and/or estrogen therapy, although approximately 10 per cent (18) to 30 per cent (11) of prostatic carcinoma patients are apparently independent of hormonal control. Bilateral adrenalectomy should benefit only patients with androgen dependent disease. The clinical prospective problem remains to objectively identify these cases. In this study we observed very poor subjective improvement in those patients subjected to adrenalectomy who had relapsed for a prolonged period from previous castration or following castration plus hypophysectomy. It could be that many of these patients exhibit a form of androgen independence as a result of such prior therapy. This is, of course, speculative at present. Nesbit *et al.*[11] found that 70% of patients who had relapsed from one form of treatment did not respond to modified or additional endocrine treatment. Patients who had relapsed from previous orchiectomy and estrogen

TABLE 5. *Twenty-four Hour Urinary Ketosteroid Excretion[3] After Bilateral Adrenalectomy in Previously Castrated-hypophysectomized Prostatic Carcinoma Patients*
(Mean Value ± S.E.M.)

	Before Adrenalectomy	After Adrenalectomy 2 Weeks	After Adrenalectomy 2 Months
Total 11-Deoxy-17-Ketosteroids	1.46 (0.4)	1.45 (0.94)	1.08 (0.26)
Total 11-Oxy-17-Ketosteroids	1.62 (0.52)	6.33 (2.19)*	6.93 (4.27)*
Total 17-Ketosteroids	3.09 (0.64)	7.78 (2.80)*	8.02 (4.10)*
N	5	3	4

N = Number of patients
* $p > 0.05$

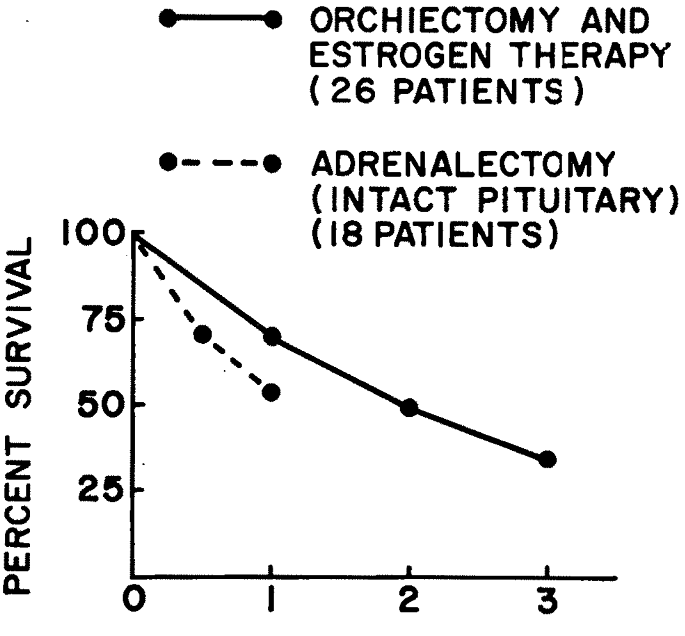


FIG. 6. The survival of patients after bilateral adrenalectomy therapy (in previous castrations) is compared with orchiectomy and estrogen therapy for disseminated prostatic carcinoma. The figures were based on survival curves using a starting point of three years after initial diagnosis.

TABLE 6. *Causes of Death Following Adrenalectomy for Advanced Prostatic Carcinoma*

Cause of Death	Group A	Group B*
Carcinomatous	7 (Case 3, 4, 5, 6, 7, 19, 20)	4 (Case 22, 23, 25, 26)
Adrenal Insufficiency	1 (Case 1)	1 (Case 24)
Myocardial infarction	1 (Case 21)	—
Septicemia	2 (Cases 2, 8)	—
Bronchopneumonia	1 (Case 9)	—

Group A—Adrenalectomy in previous castrated patients (12 patients)

Group B—Adrenalectomy in previous castrated-hypophysectomized patients (5 patients)

* One patient died from surgical complication (pulmonary emboli) and was not included for this study.

therapy may receive some benefit from adrenalectomy in 50% and 70% of cases.[8,9] There is little additional clinical information, however, to support this viewpoint.

In our observation, we found that the patients who had long periods of subjective response also had a long survival after adrenalectomy; but patients who had a poor response while suffering from metastatic disease had a short survival. This seems to confirm that adrenalectomy had some palliative effects with secondary increased survival in hormonal dependent tumors. Five patients in our series who had adrenalectomy a short period of time (2–4 months) after previous castration and no relapse, had remarkably prolonged survival time and clinical improvement (about 80%), when compared with patients who had previously relapsed (25%) (Table 2). Due to the small number of patients, this cannot, however, be regarded as conclusive.

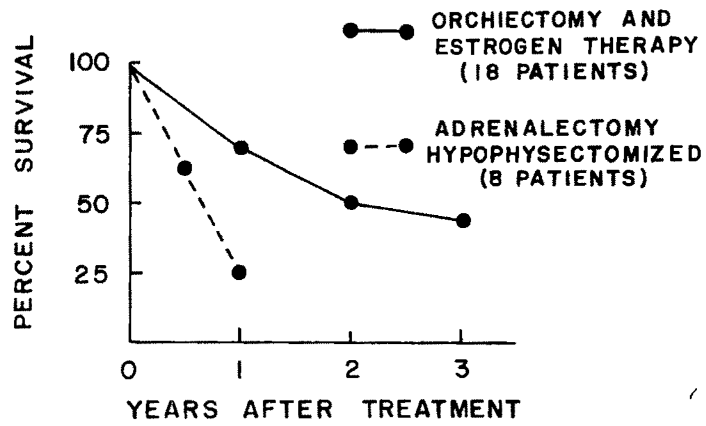


FIG. 7. The survival of patients after bilateral adrenalectomy (in castration and hypophysectomy) is compared with orchiectomy and estrogen therapy for disseminated prostatic carcinoma. The figures were based on survival curves using a starting point of four years after initial diagnosis. The first group (8 patients) had been castrated before adrenalectomy, but of eight patients adrenalectomy were performed after hypophysectomy in five patients and before in three patients.

The one year survival of patients after adrenalectomy (pituitary intact) was about 53% in this series as compared to 70% of the patients (Stage D) who had been treated by orchiectomy and estrogen and were still alive after a period of three years (Fig. 6). In contrast, the patients who were treated by bilateral adrenalectomy who had relapsed from progressive disease following castration and hypophysectomy had a one year survival of 25%, compared to 72% of Stage D patients who had been treated with orchiectomy and estrogen for a four year period and were in a clinical remission state (Fig. 7). Thus, the results in terms of survival following relapse of endocrine control for advanced disease are difficult to compare to those in patients with advanced disease who remain in endocrine control.

These studies demonstrate that a significant degree of extended survival and palliation may be achieved in some patients who have relapsed following conventional endocrine therapy when adrenalectomy is performed early after such an event. Little response was noted in patients who had subsequently been treated by hypophysectomy prior to adrenalectomy. The clinical problem to date remains to identify in advance which patient will be significantly benefited by such treatment.

Summary and Conclusion

Twenty-six patients who had proven disseminated prostatic carcinoma were treated by bilateral adrenalectomy and were critically evaluated. Sixteen patients who had relapsed from prior castration had subjective improvement varying for 3 months at 62.5% to 12 months at 25%. Poor survival was noted in patients who had relapsed from prior castration followed by hypophysectomy. A 1 year survival in patients with previous castration was observed (53%). Only 25% of those patients previously castrated-hypophysectomized had a one year survival. A definite reduction of serum acid phosphatase after adrenalectomy correlated with clinical improvement although no consistent change of total urinary 17-ketosteroids or plasma testosterone was observed. Those patients who exhibited signs of remission following adrenalectomy demonstrated a consistent reduction in the 24-hour excretion of 11-deoxy-17-ketosteroids. Further improved results following adrenalectomy for relapsed advanced prostatic carcinoma may be clinically sought in those patients who exhibit an endocrine dependent tumor.

References

1. Baker, W. J.: Bilateral Adrenalectomy for Carcinoma of the Prostate Gland: Preliminary Report. J. Urol., **70**(2):275, 1953.
2. Fergusson, J. D.: Total Adrenalectomy for Malignant Disease of the Prostate and Breast. Proc. R. Soc. Med., **47**:1007, 1954.
3. Haahti, E. O. A., VandenHeuvel, W. J. A., and Horning, E. C.: Separation of Urinary 17-Ketosteroids by Gas Chromatography. Anal. Biochem., **2**:182, 1961.
4. Harrison, J. H., Thorn, G. W., and Jenkins, D.: Total Adrenalectomy for Reactivated Carcinoma of the Prostate. N. Engl. J. Med., **248**:86, 1953.
5. Huggins, C. and Bergenstal, D. M.: Effect of Bilateral Adrenalectomy on Certain Human Tumors. Proc. Nat. Acad. Sci., **38**:73–76, 1952.
6. Huggins, C., Hodges, C. V.: Studies on Prostatic Cancer. I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. Cancer Res., **1**:293, 1941.
7. Huggins, C. and Scott, W. W.: Bilateral Adrenalectomy in Prostatic Cancer. Ann. Surg., **122**:1031, 1945.
8. MacFarlane, D. A., Thomas, L. P., and Harrison, J. H.: A Survey of Total Adrenalectomy in Cancer of the Prostate. Am. J. Surg., **99**:562, 1960.
9. Morales, P. A., Brendler, H., and Hotchkiss, R. S.: The Role of the Adrenal Cortex in Prostatic Cancer. J. Urol., **73**(2): 399, 1955.
10. Murphy, G. P., Reynoso, G., Schoonees, R., Gailani, S., Bourke, R., Kenny, G. M., Mirand, E. A., and Schalch, D. S.: Hypophysectomy and Adrenalectomy for Disseminated Prostatic Carcinoma. J. Urol., **105**:817, 1971.
11. Nesbit, R. M. and Baum, W. C.: Endocrine Control of Prostatic Carcinoma. JAMA, **143**(15):1317, 1950.
12. Pyrah, L. N.: Bilateral Adrenalectomy in the Treatment of Mammary and Prostatic Cancer. Proc. R. Soc. Med., **47**: 1002, 1954.
13. Reynoso, G. and Murphy, G. P.: Adrenalectomy and Hypophysectomy in Advanced Prostatic Carcinoma. Cancer, **29**(4):941, 1972.
14. Scardino, P. L., Prince, C. L., and McGoldrick, T. A.: Bilateral Adrenalectomy for Prostatic Cancer. J. Urol., **70**(1):100, 1953.
15. Scott, W. W. and Vermeulen, C.: Studies on Prostatic Cancer. J. Clin. Endocrinol., **2**:450, 1942.
16. Schoonees, R., Schalch, D. C., Reynoso, G., and Murphy, G. P.: Bilateral Adrenalectomy for Advanced Prostatic Carcinoma. J. Urol., **108**(1):123, 1972.
17. Taylor, S. G., III, Li, M. C., Eckles, N., Slaughter, D. P., and McDonald, J. H.: Effect of Surgical Addison's Disease on Advanced Carcinoma of the Breast and Prostate. Cancer, **6**:997, 1953.
18. Whitmore, W. F., Jr., Randall, H. T., Pearson, O. H., and West, C. D.: Adrenalectomy in the Treatment of Prostatic Cancer. Geriatrics, **9**:62, 1954.

Ruptured Appendicitis in Femoral Hernias:

Report of Two Cases and Review of the Literature

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HERNIATION of portions of the intestinal tract into femoral hernias is less common than the omentum. Small gut, colon, Meckle's diverticulum,[6] and even stomach,[11] have been found in the sac. Herniation of the appendix into a femoral hernia is rare: Wakeley[12] reports an incidence of less than one per cent in a personal series of 655 femoral hernia repairs. Inflammation of a femoral canal appendix is even less common; De Garengot[3] is credited with the first case report in 1731. In 1735 Amyand[1] carried out the first recorded appendectomy by removing a perforated appendix in an inguinal hernia. In 1954 Ryan[10] collected 537 hernias containing the vermiform appendix; 0.13 per cent of all cases of acute appendicitis occur in a hernia. By 1968, 240 cases of the vermiform appendix in a femoral hernia were collected.[5] We reviewed the English language literature and found 59 cases of acute appendicitis in a femoral hernia. In only 5 of these cases had the appendix ruptured inside the femoral hernia.[2,4,7,8,13] We have treated 2 such patients, bringing the total to 7. Table 1 briefly summarizes these patients.

Case Reports

Patient 1. A 59–year–old housewife was referred for investigation of a right inguinal sinus tract. Fifteen years before admission she had noted the appearance of a tender mass in the right groin which drained spontaneously and then healed. The mass became inflamed again 13 years later, and was at this time diagnosed as an inguinal abscess and drained surgically. A draining sinus persisted for the next 2 years. On admission the only remarkable finding was a chronic fistula in the right groin, discharging some odorless fluid. No inflammation or skin digestion was seen. A barium examination of the small bowel revealed normal ileum and cecum, and an appendico-cutaneous fistula. An appendectomy, excision of the fistula tract, and repair of the femoral hernia were carried out. Fig. 1 shows the operative findings. The right groin has remained healed for a 15 year follow-up period.

Patient 2. A 76–year–old diabetic lady was admitted with an inflamed right groin mass of unknown duration. There had been no change in gastrointestinal function; examination revealed a confused dehydrated lady in diabetic ketoacidosis. There was a crepitant right groin swelling with cellulitis extending from the right labium major to the anterior superior iliac spine and down the medial side of the thigh. The overlying skin showed blebs and necrotic areas. Fig. 2 shows an X-ray demonstrating subcutaneous emphysema. Bowel sounds were normal. Following resuscitation with fluids, electrolytes, insulin and antibiotics she was taken to the operating room where wide excision of necrotic tissue was carried out. Fig. 3 shows the operative findings. A perforated appendix was found in the femoral canal and a transabdominal appendectomy was carried out. The hernial site was packed open. After an initial difficult post-operative course, she recovered, began to eat, and formed granulation tissue in the wound. She died suddenly on the 11th post-operative night. Blood cultures were sterile and an autopsy failed to reveal the cause of death.

Discussion

Because of its rarity and atypical presentation, the correct diagnosis in this condition is difficult and seldom made. Of the 59 reported cases of appendicitis in a femoral hernia, only one author claims to have made the correct diagnosis pre-operatively,[9] and in none of the cases with a ruptured appendix has the correct diagnosis been made initially. In our first patient, a barium meal enabled the diagnosis to be made before definitive surgery, but when first seen, she was also thought to have a groin abscess and was drained as such.

Our patients illustrate the acute (patient 2) and chronic (patient 1) presentation of this rare lesion. It is a

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Reprint requests to Dr. R. L. Estrada at the above address.

TABLE 1. *Clinical Features of Reported Ruptured Appendicitis in Femoral Hernias*

Author	Year	Sex	Age	Site	Duration of Symptoms
Waring[13]	1891	F	46	right groin	2 years chronic 1 day acute
Hodgson[7]	1925	F	70	right groin	8 months
Holliday[8]	1953	F	57	right groin	2 weeks
Carey[2]	1967	M	48	right groin	5 months chronic 5 days acute
Gerami[4]	1970	M	71	right groin	5 months
Voitk	1973	F	59	right groin	15 years
Voitk	1973	F	76	right groin	unknown—? 6 months

disease of post-menopausal women. The youngest patient previously reported (Table 1) is 46; our first patient, although 59 when first seen by us, was 44 at the time of her first symptoms. Femoral hernia occurs with a female: male sex ratio of 6:1. The sex ratio in the 59 reported cases of appendicitis in femoral hernias is similar. Female predominance persists in the cases of ruptured appendicitis in femoral hernias, but is less pronounced probably because of the small number of cases. Thus one may conclude that the incidence of herniation of the appendix into femoral hernias, its inflammation and rupture is similar in both sexes and parallels the incidence of femoral hernias.

It is interesting to speculate whether the appendicitis arises spontaneously or secondarily to obstruction at the hernial neck. In any case, the tight neck serves to wall off the disease and thus often prevents the generalised

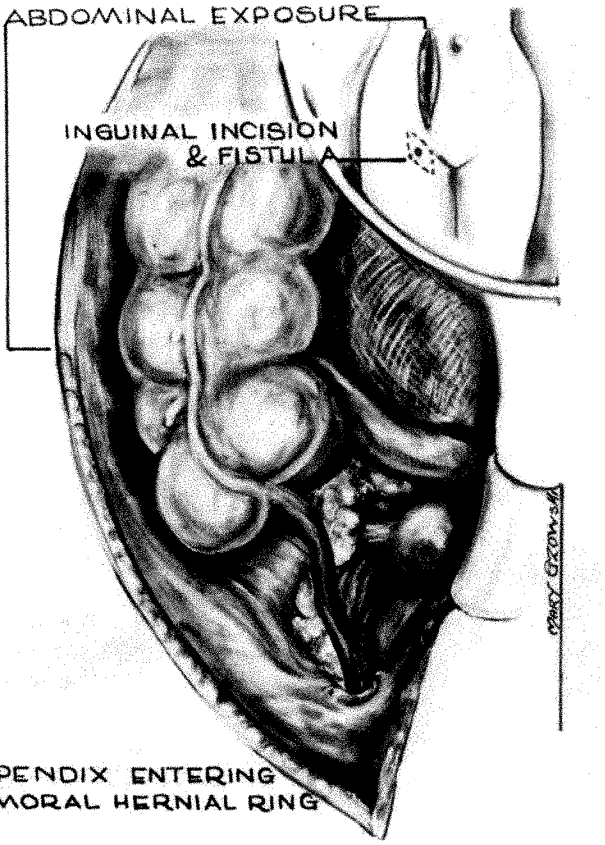

ABDOMINAL EXPOSURE
INGUINAL INCISION & FISTULA
APPENDIX ENTERING FEMORAL HERNIAL RING

FIG. 1. Artist's sketch of operative findings in case 1. The appendix is adherent to the femoral canal and a well-established fistula is completely isolated from the abdominal cavity.

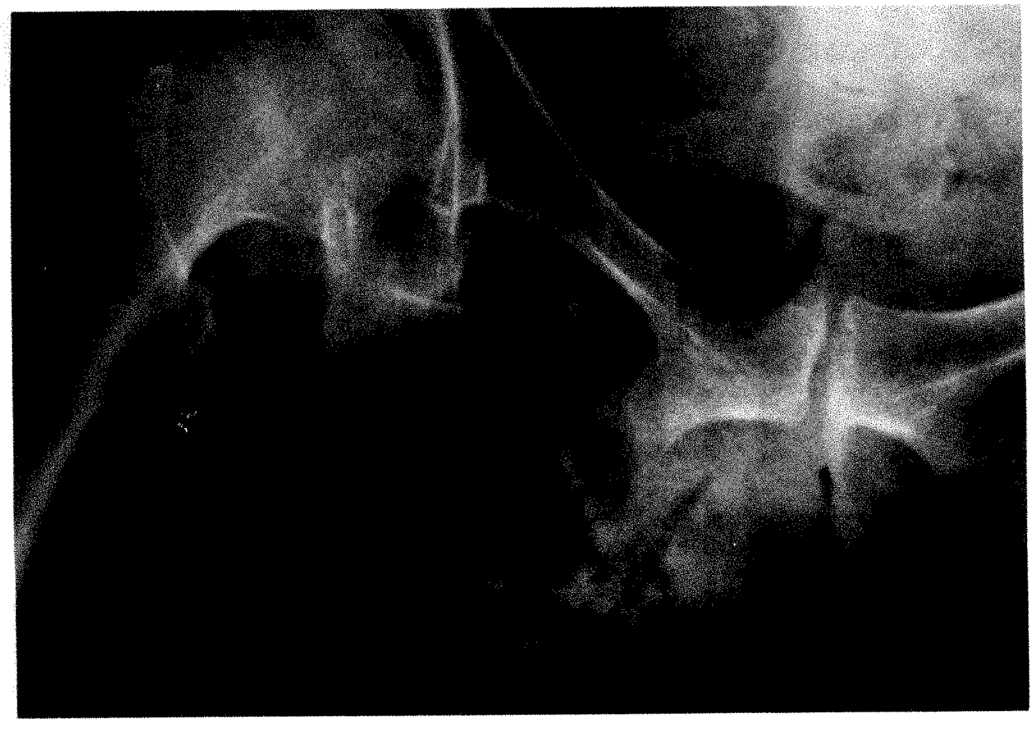


FIG. 2. X-ray of the lesion in patient 2 on admission. The presence of subcutaneous emphysema should alert the physician to ruptured bowel communicating with the subcutaneous tissues.

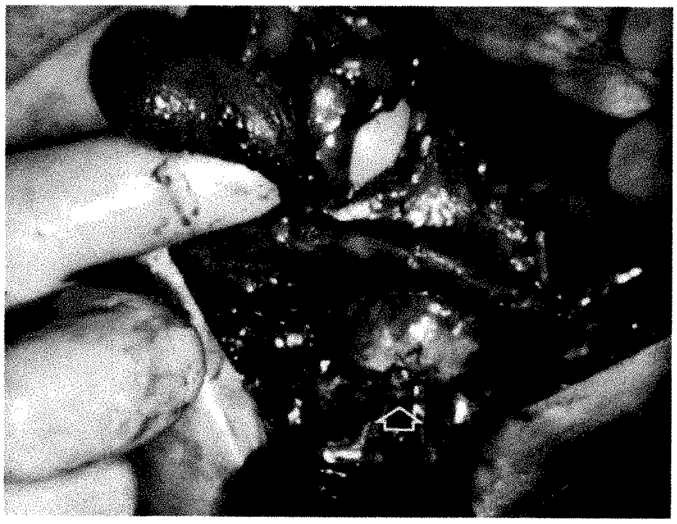


FIG. 3. Operative findings of patient 2. A large amount of necrotic and gangrenous tissue had to be excised. The cecum and proximal normal appendix are demonstrated through the abdominal portion of the wound by the surgeon's hand. Note the similarity of this to the findings of Fig. 1. The appendix is fixed to the femoral canal. The grey mass medially below the inguinal ligament is the swollen gangrenous distal portion of the appendix with a ruptured tip (arrow).

abdominal signs of appendicitis. Upon rupture of the organ, peritonitis does not result. Because the appendix does not interrupt bowel continuity, bowel function remains normal. The localized rupture soon expresses itself as a soft tissue infection leading to abscess formation. Gas producing organisms do not cause spontaneous abscesses. Thus, the finding of subcutaneous gas, a "wind abscess," must indicate ruptured bowel, and if bowel function is present, the appendix is a likely source. In our second patient, additional gas may have been produced by gas-forming organisms released following rupture, as the condition was a long-standing one due to patient's self-neglect. Coliforms only were grown on culture, but smears revealed both gram negative and gram positive bacilli. If drainage is established, whether spontaneously or surgically due to misdiagnosis, the condition follows a very benign and innocuous course. This is well illustrated by our first patient who did not manifest any of the toxic and life-threatening signs seen in the second patient. A recurrent or persistent fistula can be definitively dealt with on an elective basis and a hernia repair effected at the same time.

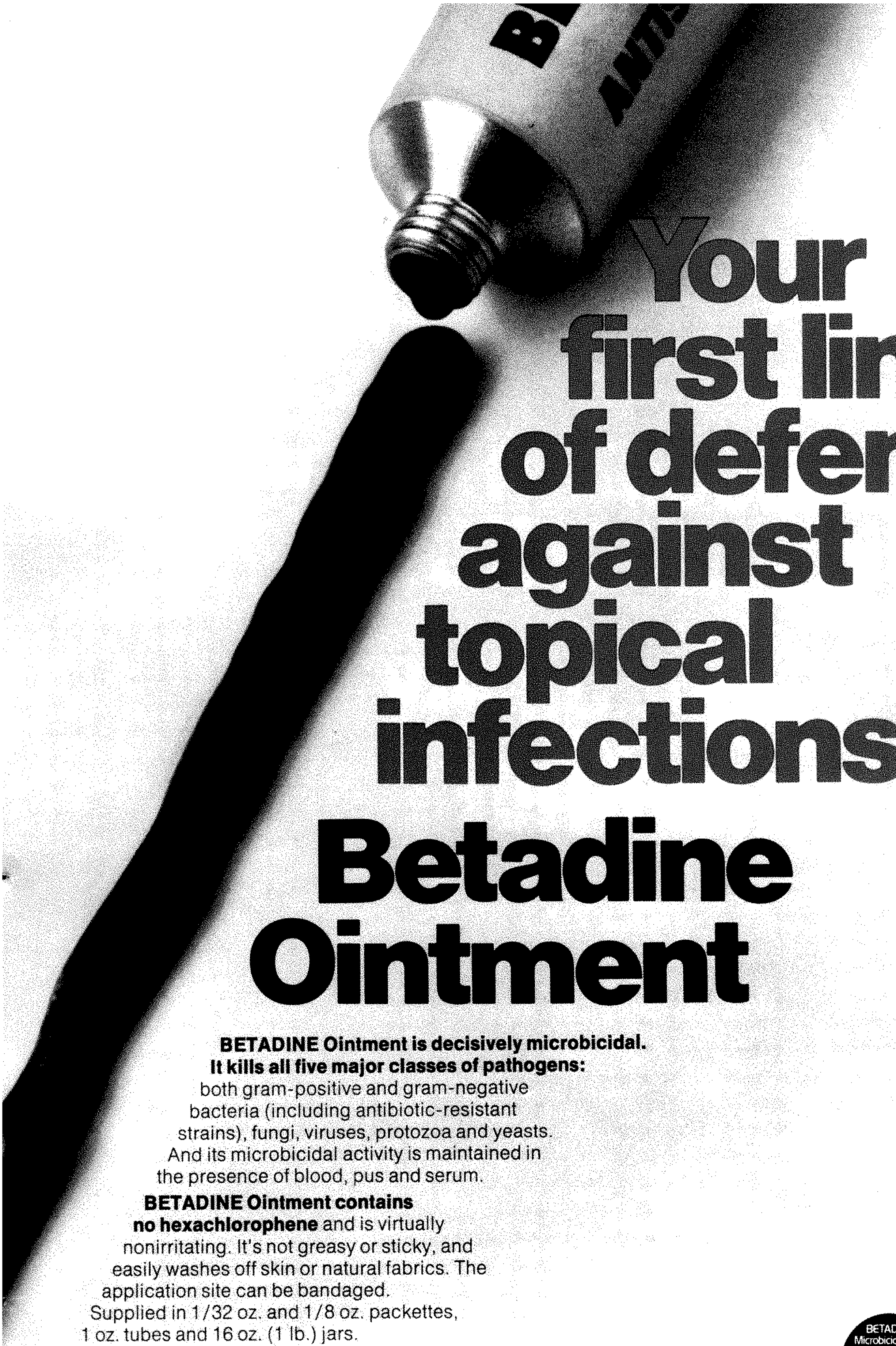
Appendicitis in a femoral hernia should be suspected if a similar mass is found on the left side, as the appendix has been found in the left femoral hernial sac in the presence of a mobile cecum.[13] This could also occur if the patient has non-rotation of the mid gut loop or situs inversus abdominalis.

Summary and Conclusions

1. Ruptured appendicitis in a femoral hernia is very rare. The 5 cases previously reported in the English language literature are reviewed and two new cases are added.
2. This condition is frequently misdiagnosed. The typical patient is a post-menopausal woman, although 2 of the reported cases are men, with an inflammatory mass in the right groin demonstrating subcutaneous gas in the presence of normal bowel function.
3. If misdiagnosed as an abscess, early incision and drainage may be life-saving. The ensuing fecal fistula may be electively treated by fistulectomy, appendectomy and herniorraphy when diagnosed.

References

1. Amyand, C.: Of an Inguinal Rupture, with a Pin in the Appendix Coeci, Incrusted with Stone; and Some Observations on Wounds in the Guts. Phil. Trans. Royal Soc., **39**: 329, 1736.
2. Carey, L. C.: Acute Appendicitis Occurring in Hernias: A Report of 10 Cases. Surgery, **61**:236, 1967.
3. De Garengot, cited by Garland, E. A.: Femoral Appendicitis. J. Indiana Med. Assoc., **48**:1292, 1955.
4. Gerami, S., Easley, G. W. and Mendoza, C. B. Jr.: Appendiceal Abscess as Contents of Right Femoral Hernia. A Case Report. Internat. Surg., **53**:354, 1970.
5. Griffin, J. M.: Incarcerated Inflamed Appendix in a Femoral Hernia Sac. Am. J. Surg., **115**:364, 1968.
6. Harf, A.: Einklemmung des Meckelschen Divertikels in einer Schenkelhernie. Deutsche Med. Wochenschr., **45**:881, 1919.
7. Hodgson, N.: Strangulated Femoral Hernia Associated with an Appendix Abscess in the Hernial Sac. Brit. J. Surg., **13**:386, 1925.
8. Holliday, T. D. S. and White, J. R. A.: Inflamed Appendices in Femoral Hernial Sacs. Brit. Med. J., **11**:779, 1953.
9. Powell, H. D. W.: Gangrenous Appendix in Femoral Hernial Sac. Lancet, **267**:1211, 1954.
10. Ryan, W. J.: Hernia of the Vermiform Appendix. Ann. Surg., **106**:135, 1937.
11. Spiegel, B.: Einklemmung des Magens im Schenkelbruch. Zentalbl F. Chir., **47**:373, 1920.
12. Wakeley, C. P. G.: Hernia of the Vermiform Appendix. *In* Maingot R: Abdominal Operations. New York, Appleton-Century-Crofts, 1969, p. 1288.
13. Waring, H. J. and McAdam Eccles, W.: Cases from Mr. Langton's Wards. St. Bart's Hosp. Rep., **27**:179, 1891.



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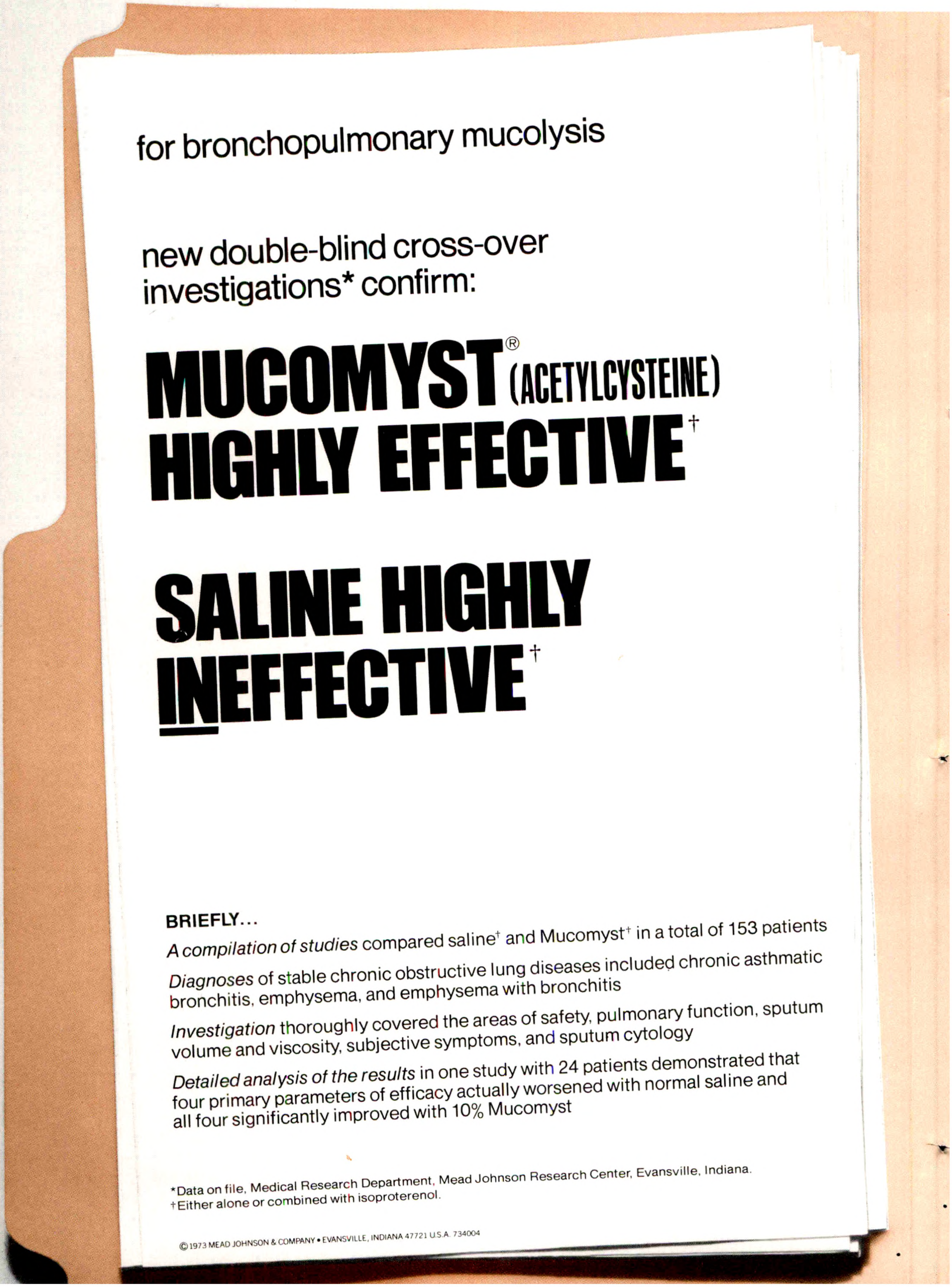

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[*] Data on file, Medical Research Department, Mead Johnson Research Center, Evansville, Indiana.

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	Variables	
	Improved	Worsened
Mucomyst	13	2
Saline	4	5

CONCLUSIONS
- Mucomyst decreases sputum viscosity—saline *at best* effects no change
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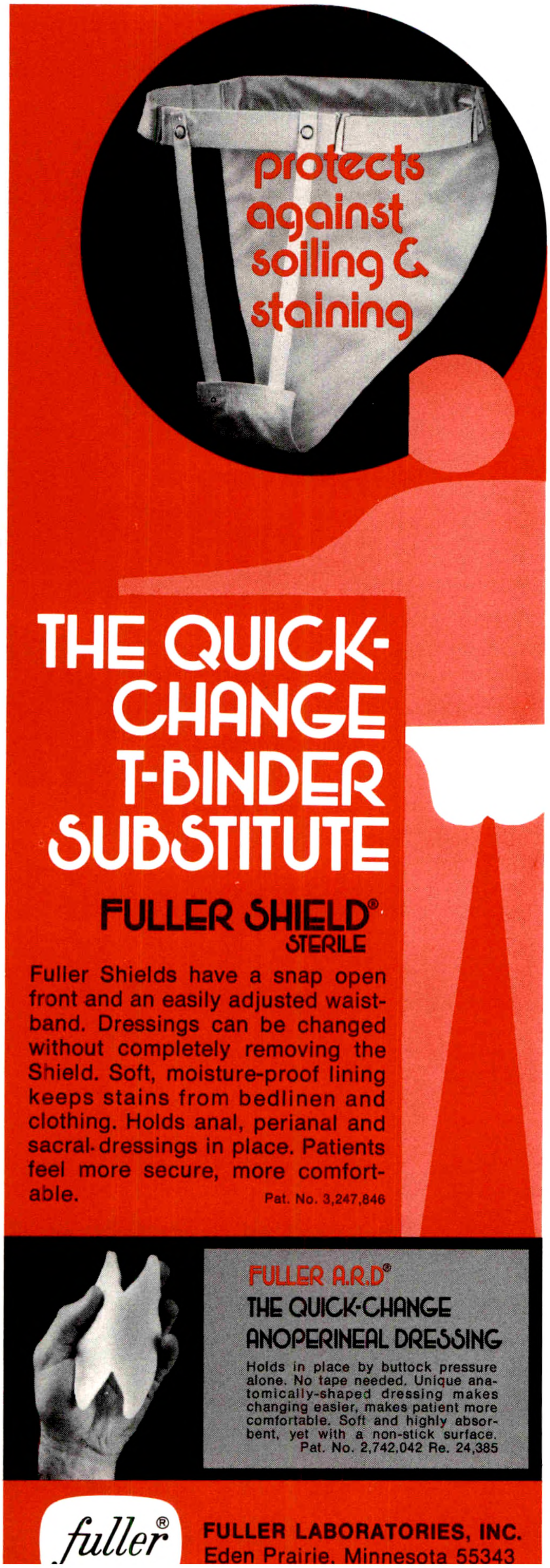

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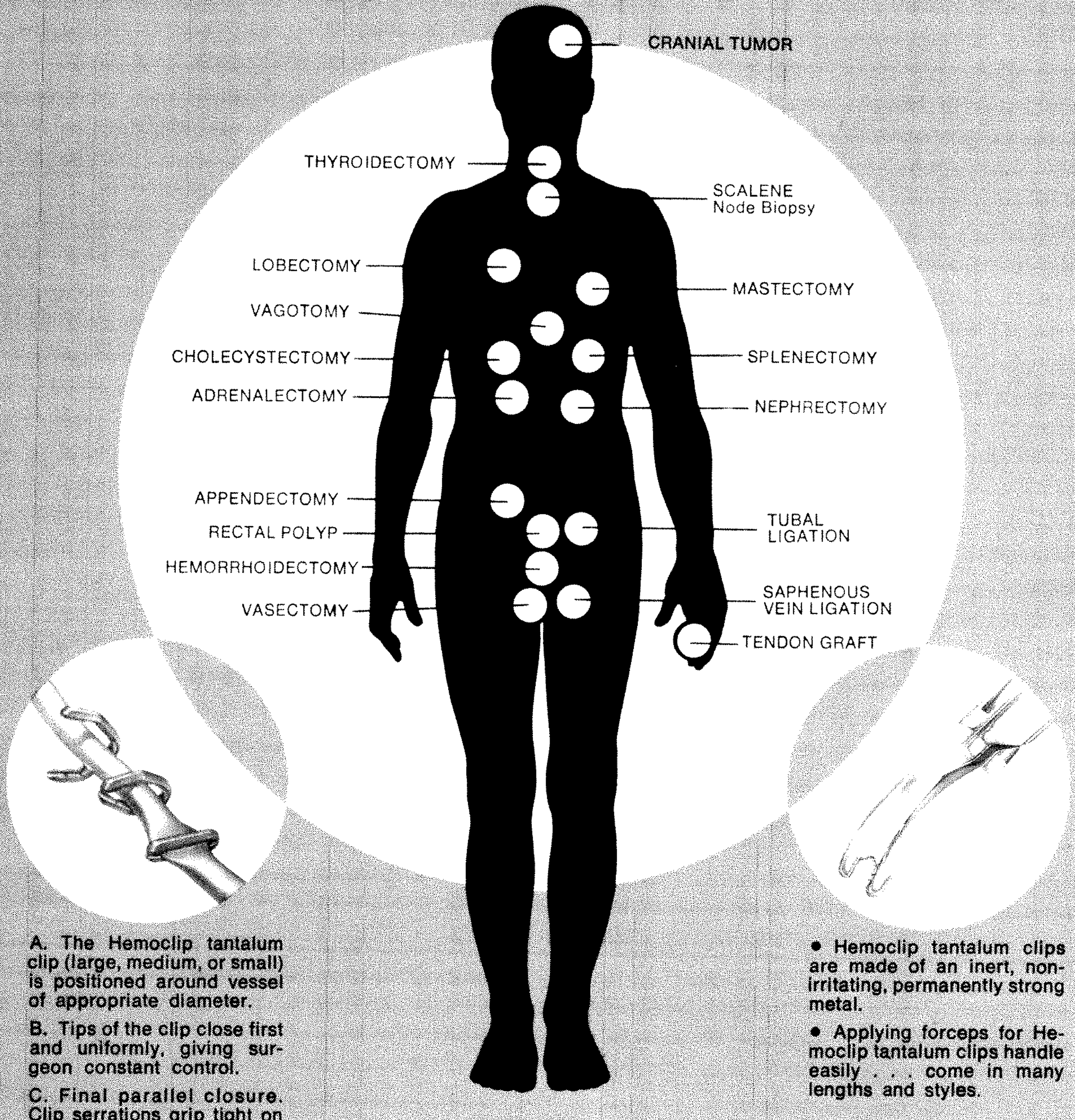
Modern method of hemostasis, ideal in virtually all surgical procedures, proved quick and effective time and again in these specific operations:



A. The Hemoclip tantalum clip (large, medium, or small) is positioned around vessel of appropriate diameter.

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- Hemoclip tantalum clips are made of an inert, non-irritating, permanently strong metal.
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EDWARD WECK & COMPANY, INC. • 49-33 31st Place, Long Island City, N.Y.11101

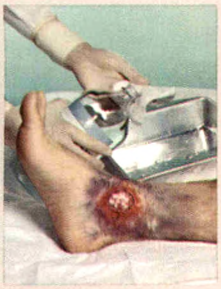
adjunctive therapy for wound debridement

HELPS TO REMOVE:

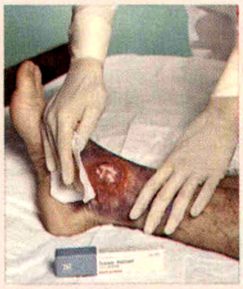
- Necrotic Tissue and Associated Odor

HELPS PREPARE WOUND FOR:

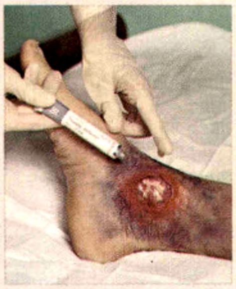
- Granulation/Healing
- Granulation/Grafting



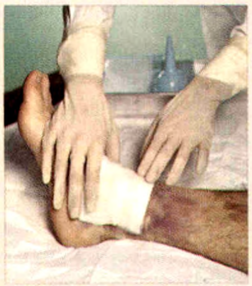
CLEANSE WOUND
Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials.



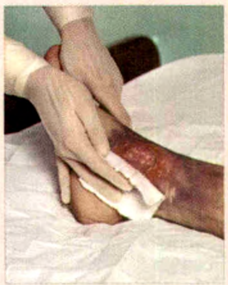
THOROUGHLY MOISTEN
Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g., sodium chloride or water solutions).



APPLY ENZYME
Apply a layer of TRAVASE Ointment. Assure intimate contact with necrotic tissue and complete wound coverage.



APPLY MOIST DRESSING
Apply loose moist dressings (most important with dry leathery eschar).



CHANGE DRESSINGS
When changing dressing, gently wipe away the dissolved material. Repeat the procedure, including application of TRAVASE Ointment, 3 to 4 times per day for best results.

Travase® Ointment
brand of Sutilains

Travase® Ointment
brand of **Sutilains**

Description
TRAVASE® (brand of sutilains) Ointment is a sterile preparation of
proteolytic enzymes, elaborated by Bacillus subtilis, in a hydro-
phobic ointment base consisting of 95% white petro
polyethylene. One gram of ointment
casein units* of protea

wound healing (4).
temperatures these proteolytic enzymes have optimal
activity in the pH range from 6.0 to 6.8.

Indications
For wound debridement (1,2)—TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

Second and third degree burns,
Decubitus ulcers.
Incisional, traumatic, and pyogenic wounds,
Ulcers secondary to peripheral vascular disease.

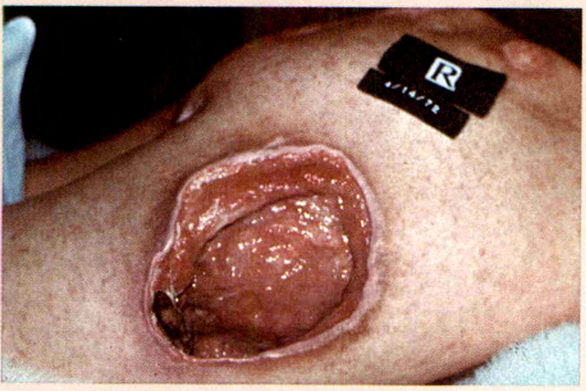
FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Please see next page for prescribing information.

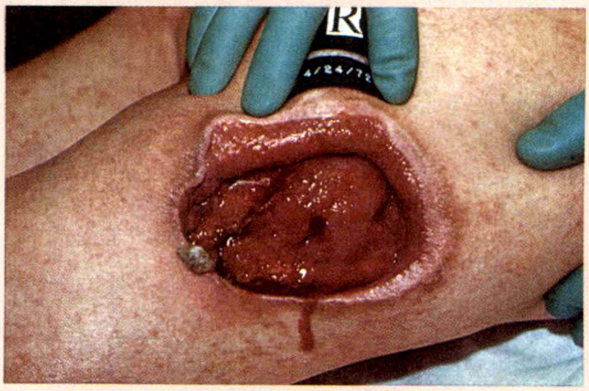
Travase® Ointment brand of Sutilains

ulcers

TERRY V. CARLE, M.D., CLINICAL INSTRUCTOR, DEPT. OF PHYS. MED. & REHAB.,
CRAIG REHABILITATION HOSPITAL, UNIVERSITY OF COLORADO



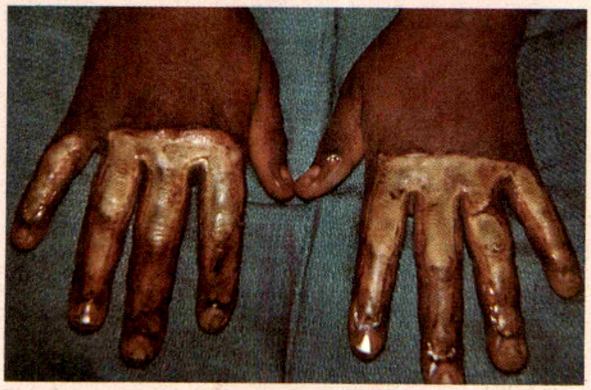
Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



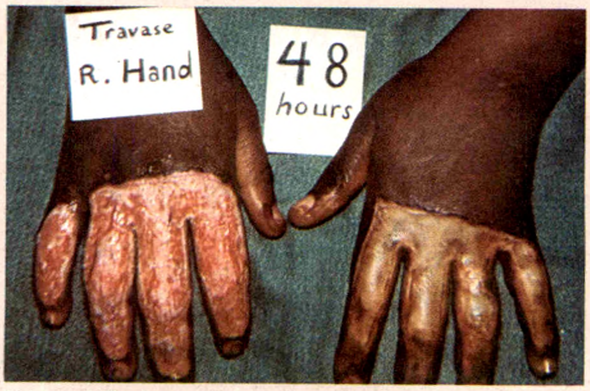
After nine days of TRAVASE therapy, debridement is nearly complete and granulation evident.

burns

DALE B. DUBIN, M.D., DIPLOMATE,
AMERICAN BOARD OF PLASTIC SURGERY, TAMPA, FLORIDA



Before treatment . . .



48 hours following treatment with TRAVASE Ointment on right hand; left hand is control.

Travase® Ointment

(brand of Sutilains)

Indications: For wound debridement, TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

- Second and third degree burns,
- Decubitus ulcers,
- Incisional, traumatic, and pyogenic wounds,
- Ulcers secondary to peripheral vascular disease.

Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

- Wounds communicating with major body cavities,
- Wounds containing exposed major nerves or nervous tissue,
- Fungating neoplastic ulcers,
- Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE upon the developing fetus.

Warning: Do not permit TRAVASE Ointment to come into contact with the eyes. If contact is made, immediately rinse with copious amounts of water, preferably sterile.

Precautions: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents (see package insert). Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

DOSAGE AND ADMINISTRATION: STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT:

1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g. sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

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DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

New from SK&F...

ANCEF®

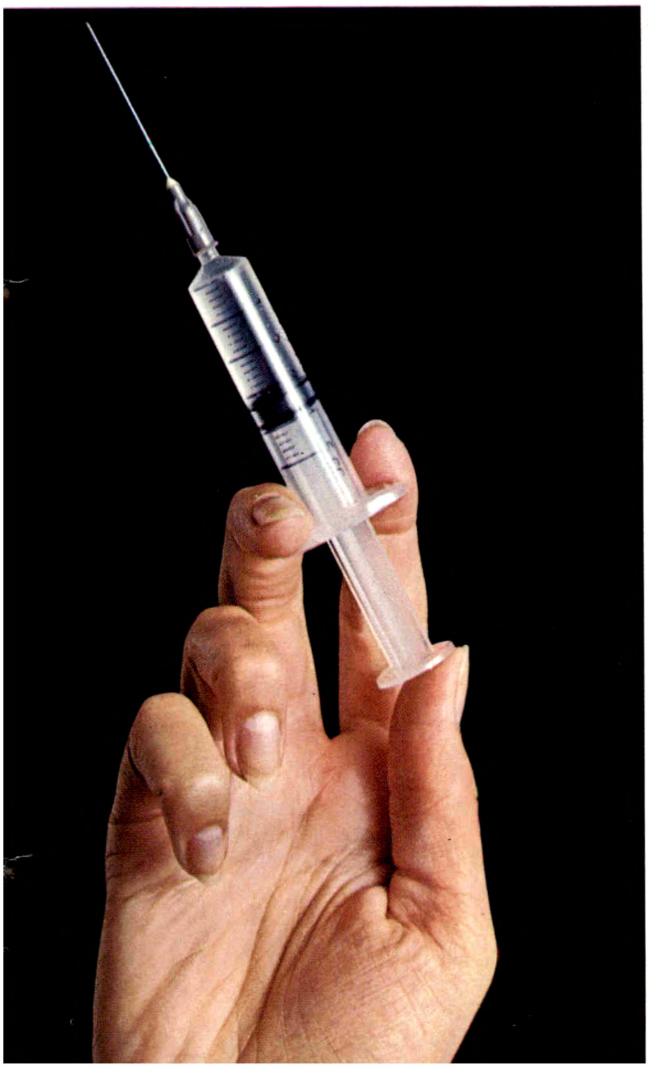
STERILE CEFAZOLIN SODIUM brand of

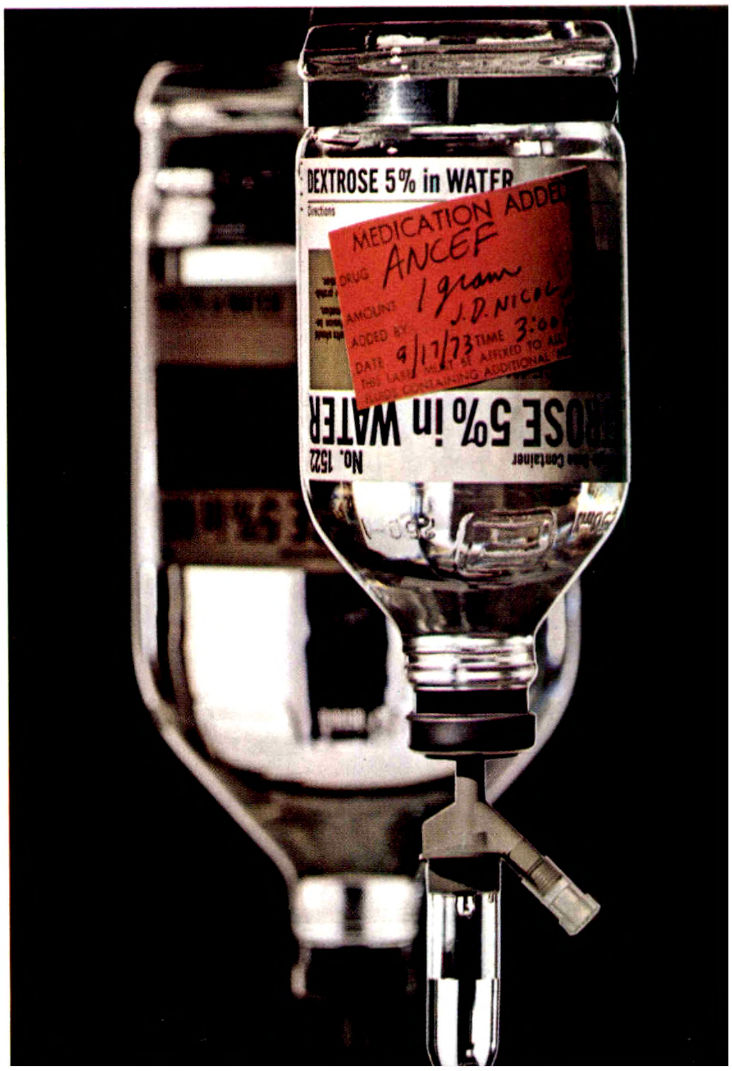
Parenteral Cephalosporin Antibiotic

Injection: 250 mg., 500 mg. and 1 gram

Please see brief summary of prescribing information on last page of this advertisement.

I.M. **Offers the convenience of I.M. or I.V. administration. Pain on injection is infrequent with 'Ancef'.** **I.V.**





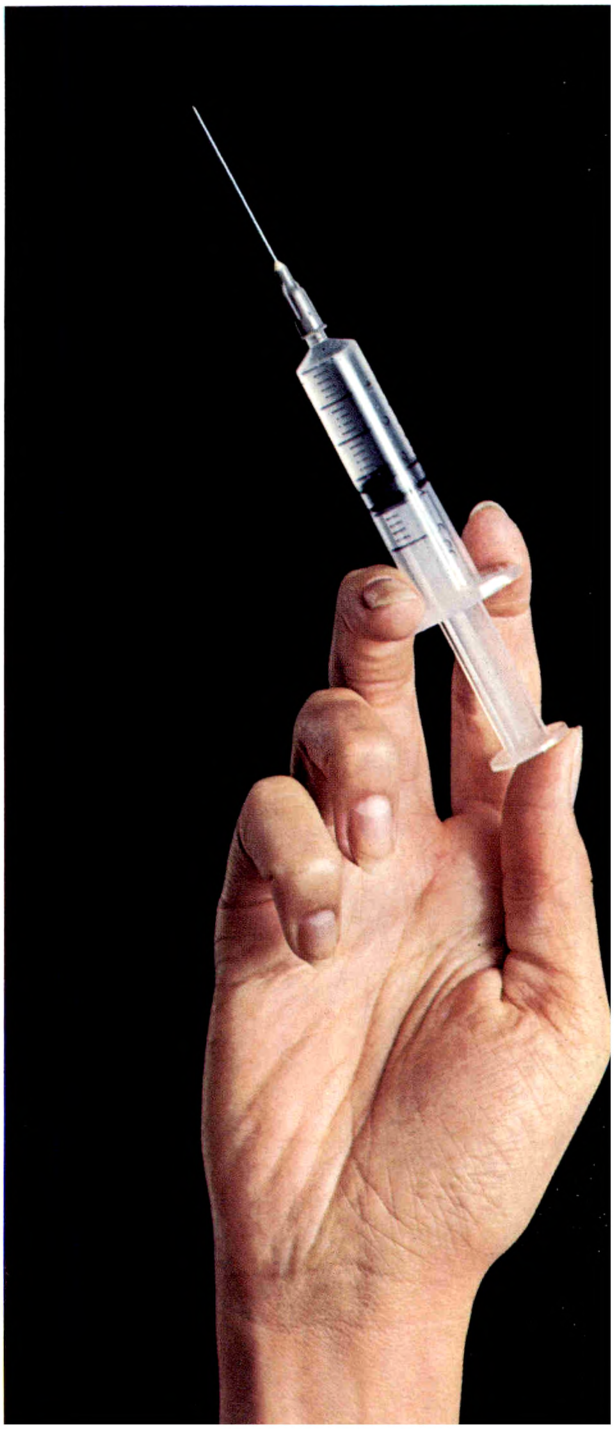
New from SK& ...

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

I.M.



By either route...

'ANCEF' produces high blood levels.

(In a 3-part crossover study in 60 adult male volunteers, following a 500 mg. I.M. injection, a serum level of 36.8 μg./ml. was achieved at 1 hour; a level of 3.0 μg./ml. was still maintained at 8 hours.)

'ANCEF' Indications

Respiratory tract infections due to *D. pneumoniae, Klebsiella* species, *H. influenzae, S. aureus* and group A beta-hemolytic streptococci.

Genitourinary tract infections due to *E. coli, P. mirabilis, Klebsiella* species and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *S. aureus,* group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus.*

Septicemia due to *D. pneumoniae, S. aureus, P. mirabilis, E. coli* and *Klebsiella* species.

Endocarditis due to *S. aureus* and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

'ANCEF' is bactericidal against the following organisms *in vitro*:

Staphylococcus aureus
(penicillin-sensitive and penicillin-resistant)
Group A beta-hemolytic streptococci and other strains of streptococci
(many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole-positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to 'Ancef'.

I.V.

ANCEF® brand of sterile cefazolin sodium has produced no nephrotoxicity in extensive clinical trials.

(Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.)

Adverse Reactions

Adverse reactions reported in the clinical trials included: pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of adverse reactions associated with 'Ancef' therapy please see brief summary of prescribing information on last page of this advertisement.

'ANCEF' Clinical Efficacy

Site of Infection	Number of Patients	% "Good" or "Excellent" Response*
Respiratory Tract	377	93%
Genitourinary Tract	544	93%
Skin and Soft Tissue	122	84%
Blood and Lymph	69	81%
Bone and Joint	35	80%
Miscellaneous and Multiple Site	34	85%

The preceding results were collected from identical clinical protocols with comparable criteria of efficacy.

*Excellent: Initial improvement at 1-3 days with maximum improvement between 3-7 days. Good: Initial improvement at 2-4 days with maximum improvement between 4-10 days.

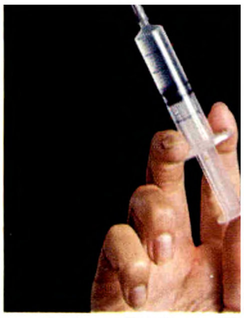
See following page for a brief summary of prescribing information including contraindications, warnings, precautions and dosage.

Now from SK&F...

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM



Before prescribing, see complete prescribing information in SK&F literature.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro*:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)
Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae	*Klebsiella* species
Escherichia coli	*Enterobacter aerogenes*
Proteus mirabilis	*Hemophilus influenzae*

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Diplococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Diplococcus pneumoniae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli*, and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'ANCEF' IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for mild gram-positive infections is 250 mg. to 500 mg. of 'Ancef' every 8 hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every 8 hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 gram of 'Ancef' every 6 to 8 hours. 'Ancef' has been administered in dosages of six grams per day in serious infections such as endocarditis. 'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.) 60% of the normal daily dose given in divided doses q12h should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.) 25% of the normal daily dose given in divided doses q12h should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.) 10% of the normal daily dose given q24h should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dose may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories, Division of SmithKline Corp., Philadelphia, Pa. 19101

Esophageal Surgery:

A Procedure for Posterior Invagination Esophagogastrostomy in One-Stage Without Positional Change

N. OKADA, M.D., T. KURIYAMA, M.D., H. UMEMOTO, M.D.,
T. KOMATSU, M.D., Y. TAGAMI, M.D.

*From the Department of Thoracic Surgery,
Wakayama Medical College, Wakayama, Japan*

In the field of esophageal surgery various techniques for esophageal reconstruction have been designed. In spite of continued efforts on the part of the surgeons, an operation for esophageal cancer still remains one of the most difficult procedures because of the high incidence of post-operative complications. Some post-operative complications such as anastomotic leak, reflux esophagitis, etc. have a close relationship with the operative procedure and therefore some complications may be prevented by an improved surgical technique.

This paper presents an operative technique entitled "posterior invagination esophagogastrostomy" and discusses the merits of this procedure in preventing some of the above mentioned complications as well as eliminating a change of body position during the resection and primary reconstruction of the esophagus.

Operative Technique

With the patient in the right lateral position, a single thoraco-abdominal incision is made in the left 6th intercostal space for a lower esophagectomy and in the left 5th intercostal space for an upper or middle esophagectomy. The costal cartilage is cut, and the diaphragm is opened to the esophageal foramen, providing a large operative field from the left thoracic cavity to the epigastric region. The distal segment of the esophagus is pulled out with a Nelaton catheter.

In cases of malignant tumors, blunt and sharp ablation of the esophagus to within 10 cm of the tumor border is performed, and at the same time the adjacent lymph-nodes are extirpated. After completing the mobilization of the stomach, the esophagus and stomach are divided near the cardia by use of the Petz sewing instrument and pyloroplasty is then carried out. The residual stomach is elevated into the thoracic cavity bringing the lesser curvature to the ventral side and the greater curvature to the dorsal side. The apex of the remaining stomach is bent forward as illustrated in Fig. 1. The proximal segment of the esophagus is placed on the posterior wall of the stomach and fixed in position with three lines of mattress sutures, each line consisting of three sutures to total nine sutures (Fig. 1). After this fixation, the distal segment of the esophagus with the lesion is excised and an all-layer anastomosis between the esophagus and the posterior wall of the stomach at a distance about 5 cm from the apex of the remaining stomach is carried out (Fig. 2). A nasal catheter is introduced into the stomach to provide nutrition and for aspiration purposes. The apex of the stomach is then extended up onto the left esophageal wall and fixed in position with several sutures in order to cover the anastomosis (Fig. 3). In this manner the anastomosed region is completely blocked from the thoracic cavity. A catheter for drainage is inserted into the thoracic cavity and the chest and abdomen are closed.

In cases of esophagogastric anastomosis at the level of the neck, the decollement of the esophagus and the moblization of the stomach are best carried out under a left fifth thoracolaparotomy. After dividing the esophagus and the stomach, a new incision is made at the left cervical region along the posterior margin of the sternocleidomastoid muscle. The entire thoracic esophagus is pulled out from the neck incision and the stomach is elevated to the cervical level through the posterior mediastinum across the aortic arch. The anastomosis between the cervical segment of the esophagus and the posterior wall

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Submitted for publication December 11, 1972.

Reprint requests to: Naniwa Okada, M.D., Department of Thoracic Surgery, Wakayama Medical College, 7-bancho 1, Wakayama-city, Japan.

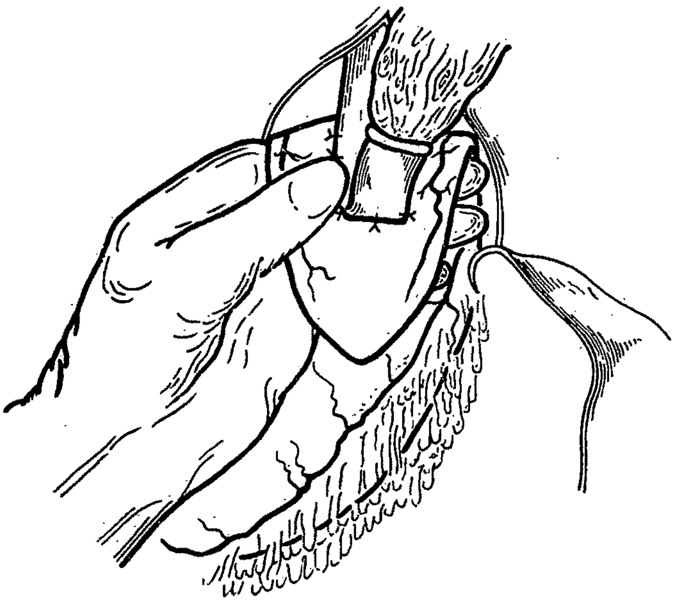

FIG. 1. The proximal segment of the esophagus is placed on the posterior wall of the stomach, and fixed in 3 lines with 3 mattress sutures. (Left lateral view.)

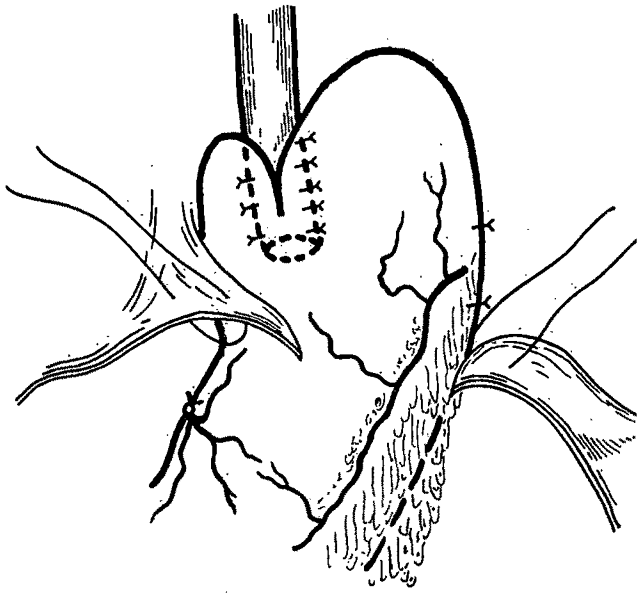

FIG. 3. The apex of stomach is extended upon the left esopha wall and fixed with several stitches to cover the anastomosis. (terior view.)

of the stomach is constructed similarly to the procedure described above.

The right lateral position of the patient remains unchanged throughout the operative procedure.

Clinical Cases

The posterior invagination esophagogastrostomy without positional change was performed on a total of 43 cases during the almost 5-year period from October 1967 to July 1972. All but one underwent the one-stage operation (Table 1).

Resection for malignancy was performed on a total of 38 cases while 5 cases had a benign condition. One case had a diverticulum in addition to esophageal cancer.

Thirty-eight cases were operated upon under thoracolaparotomy on the left and the remaining 5 underwent laparotomy. There were 6 cases of Iu (upper segment), 12 cases of Im (middle segment), six cases Ei (lower segment), and 27 cases of Ea+C (abdomi segment and cardia). In 5 cases the lesion was exten to Iu+Im, in one case to Iu+Im+Ei and in one c to Im+Ei (Table 2, Fig. 4). Anastomosis at neck l was done in four cases of Iu and in five cases of Pyloroplasty was carried out in only 28 of the 43 ca

The post-operative complications of anastomotic l and circulatory insufficiency were not encountered 42 cases of the one-stage operation and the only opera death was due to pneumonia which occurred in a

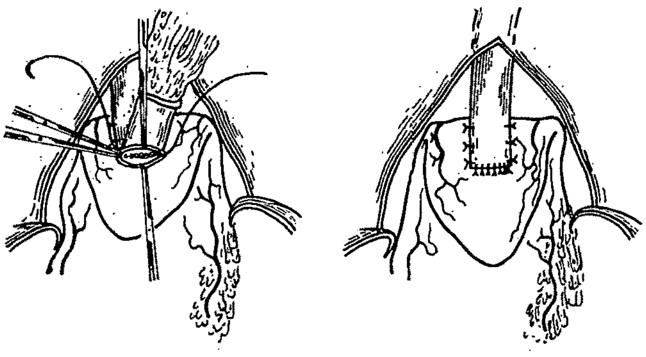

FIG. 2. The anastomosis between the esophagus and the posterior wall of stomach is carried out about 5 cm distant from the apex of the remaining stomach. (Left lateral view.)

TABLE 1. *Clinical Cases with Posterior Invagination Esoph gastrostomy*

	No. of Pati	
Esophagus		
Cancer	18	1*
Myoma	1	
Cancer plus diverticulum	1	
Cardia		
Cancer	19	
Ulcer	4	
Total	43	

* Two-stage operation

TABLE 2. *Site of Lesion*

Location	No. of Pati
Upper segment (Iu)	6
Middle segment (Im)	12
Lower segment (Ei)	6
Abdominal segment and cardia (Ea + C)	27
Total	51

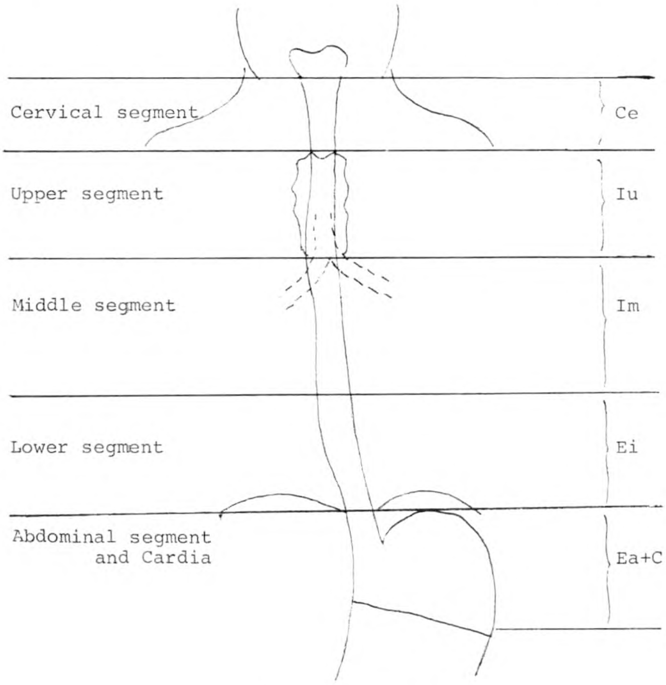

FIG. 4. Division of esophagus.

TABLE 3. *Postoperative Complications (41 Patients with One-stage Operation)*

Complication	No. of Patients
Anastomatic leak	0
Respiratory	
Atelectasis	1
Pneumonia	1*
Circulatory insufficiency	0
Stricture	3
Reflux esophagitis	8

* Operative death.

tient nine days after total thoracic esophagectomy with anastomosis at the neck level (Table 3).

The patients were examined post-operatively by radiography to examine free passage through the anastomosis and pyloric region and also were placed in various body positions to examine gastroesophageal reflux. Gastroesophageal manometrical and pH studies were also used to examine reflux. The appearance of the esophageal mucosa at the site of anastomosis was checked by use of the esophagoscope.

The following cases are representative of the technique described in this report.

Case without Pyloroplasty

1) *Case 12 (Adenocarcinoma, Ea+C, Anastomosis in Left Thoracic Cavity).* During the post-operative radiographic examination, the contrast medium descended along the lesser curvature and moved rapidly into the duodenum. A good formation of the stomach bubble was observed. No gastroesophageal reflux oc-

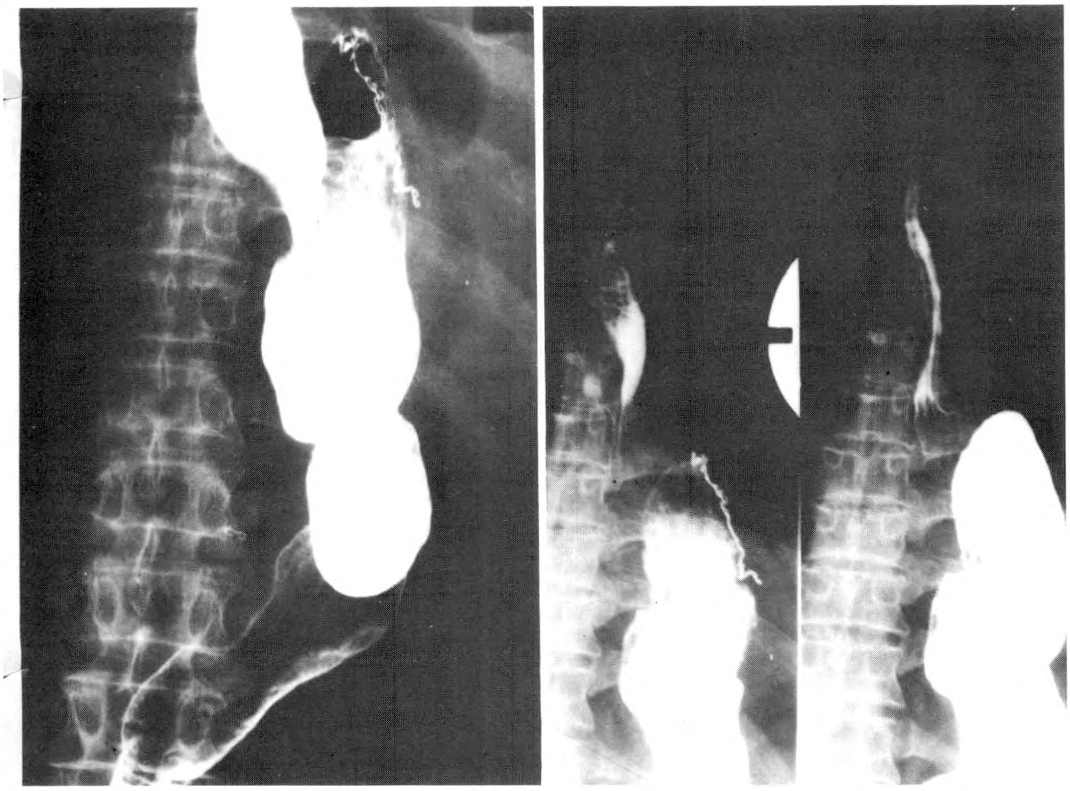

FIG. 5. Radiographs of a satisfactory anastomosis. On the left, a good formation of the stomach bubble was noticeable. On the right, reflux did not occur in a head down position of 20 degrees.

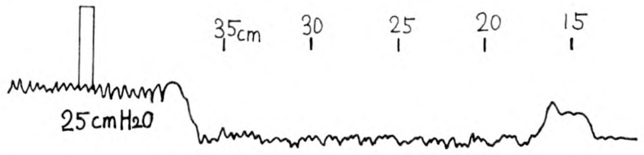

FIG. 6. Postoperative esophageal pressure showing a high pressure zone at the anastomotic area.

curred, even in head down position of about 20 degrees (Fig. 5). The gastroesophageal pressure curve showed an elevated pressure at the anastomosed area (Fig. 6).

Cases with Pyloroplasty

1) *Case 23 (Epidermoid Carcinoma Plus Esophageal Diverticulum, Iu+Im, One-stage Cervical Anastomosis).* This case had a cancer at Iu in combination with a diverticulum at Im. Anastomosis was created at the level of the neck (Fig. 7). Post-operative course was uneventful without anastomotic leak or demonstrable reflux.

2) *Case 24 (Adenocarcinoma, Ea+C, Anastomosis in Left Thoracic Cavity).* The contrast medium passed rapidly through the pylorus with a good formation of the stomach bubble. There was no reflux with the patient in head down position (Fig. 8). At the site of anastomosis, a high pressure zone was indicated by gastroesophageal pressure curve and an abrupt elevation of the pH curve was seen (Fig. 9). There was no evidence of reflux esophagitis.

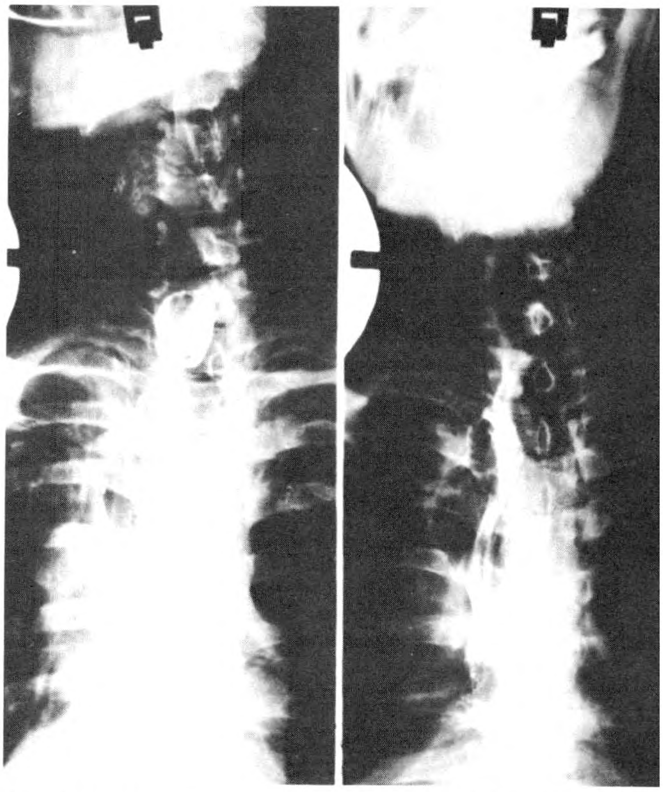

FIG. 7. Anastomosis was created at the level of the neck with n positional change. No reflux occurred.

3) *Case 26 (Epidermoid Cancer, Iu+Im+Ei, One-stage Cervical Anastomosis).* This case had a giant lesio involving the entire thoracic esophagus which radiog raphy showed to be about 20 cm in length (Fig. 10 The post-operative course was uneventful.

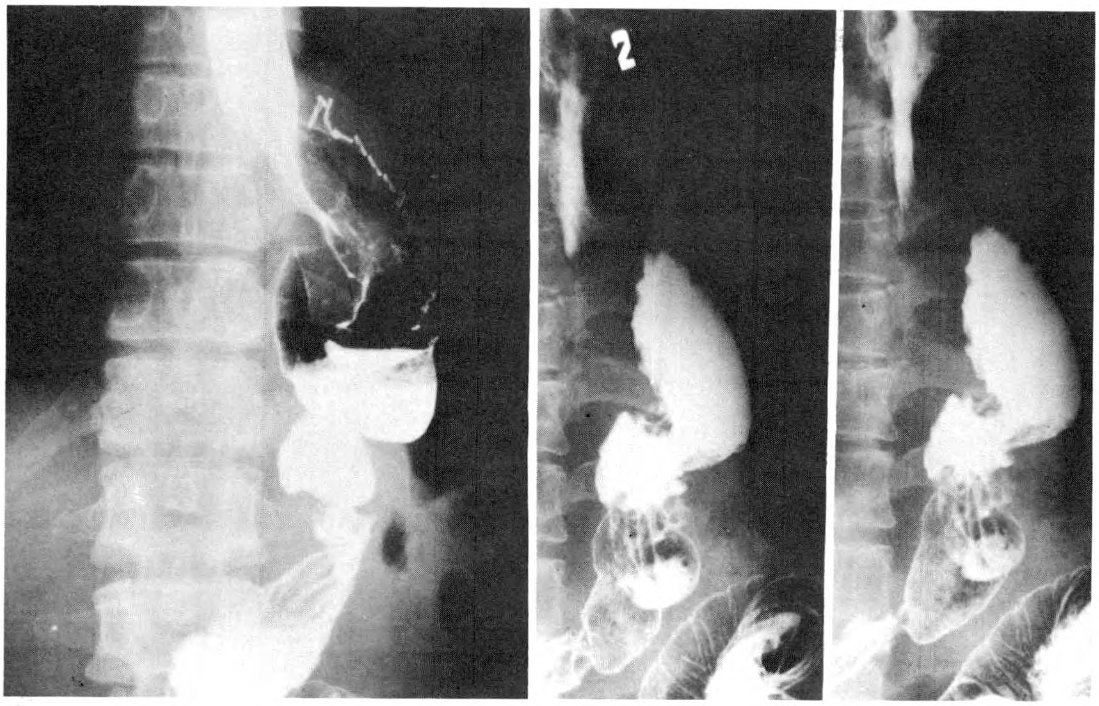

FIG. 8. On the left, a fo mation of the stomac bubble was well demon strated. On the right, th patient was positioned 2 degrees head down an the fundus was filled wit barium. Reflux could no be elicited.

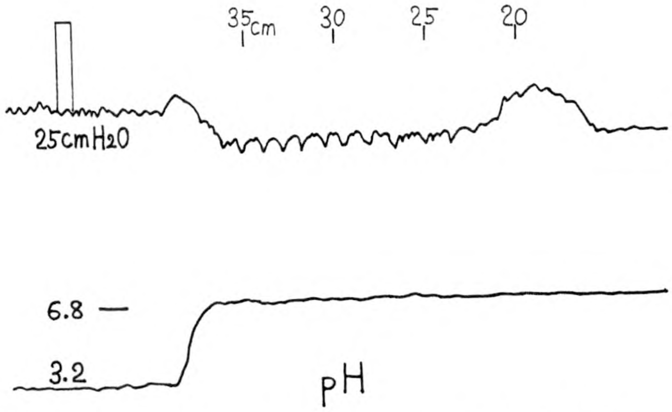

FIG. 9. Postoperative esophageal pressure and pH study show a zone of increased pressure and an abrupt rise in pH at the esophagogastric junction.

Cases with Regurgitation

1) *Case 6 (Ulcer, C, Anastomosis in the Abdominal Cavity).* The anastomosis was created near the apex of the residual stomach, but because the apex was brought to the right side of the esophagus, a physiological bubble was not formed. There was no reflux with the patient in horizontal position, but reflux developed when placed in about a 10 degree head down position (Fig. 11). The patient complained of post-operative heartburn which was relieved by medication administered over a one month period. No intragastric-intraesophageal pressure barrier was indicated six months after operation (Fig. 12).

2) *Case 21 (Epidermoid Carcinoma, Im, Left Thoracic Cavity Anastomosis).* The anastomosis was created adjacent to the lower margin of the aortic arch and the angle of His became obtuse because of the presence of the aorta between the esophagus and the gastric convexity (Fig. 13). There was regurgitation of barium with the patient in head down position.

Animal Experiments

Esophagogastrostomy was performed on adult dogs divided into four groups as shown in Table 4. Gastroesophageal reflux developed in the groups with end-to-end anastomosis, anterior and posterior wall anastomosis. Post-operative ulcers formed in these 3 groups.

In the group undergoing posterior invagination anastomosis, no evidence of reflux was observed in radiographic examination and endoscopic, intraesophageal pressure and pH studies. Histological examination one year after operation showed no evidence of ulcer formation.

Discussion

Anastomotic leak, pulmonary complication, and circulatory insufficiency are the three major post-operative complications of esophageal cancer. Among these, anastomotic leak has the most direct relation to operative technique, in spite of surgical efforts to prevent this complication.[5,6,11,20] Nakayama[12] reported a 20% incidence of this complication and Nabeya[10] reported an 11.7% incidence in his cases.

In the present series of 42 cases undergoing posterior invagination anastomosis in a one-stage operation, the absence of anastomotic leak is attributed to the following factors:

1) The anastomosis was constructed on the posterior wall of the mobilized stomach which is an area with sufficient blood flow.

2) The anastomosed area was invaginated and completely blocked from the thoracic cavity.

3) Tension on the suture line of the anastomosis was avoided.

4) The wide field of operation.

Reflux esophagitis is another important surgical problem and among the numerous techniques designed to prevent this complication, Ellis and co-workers[3] carried out pyloroplasty for early elimination of the gastric

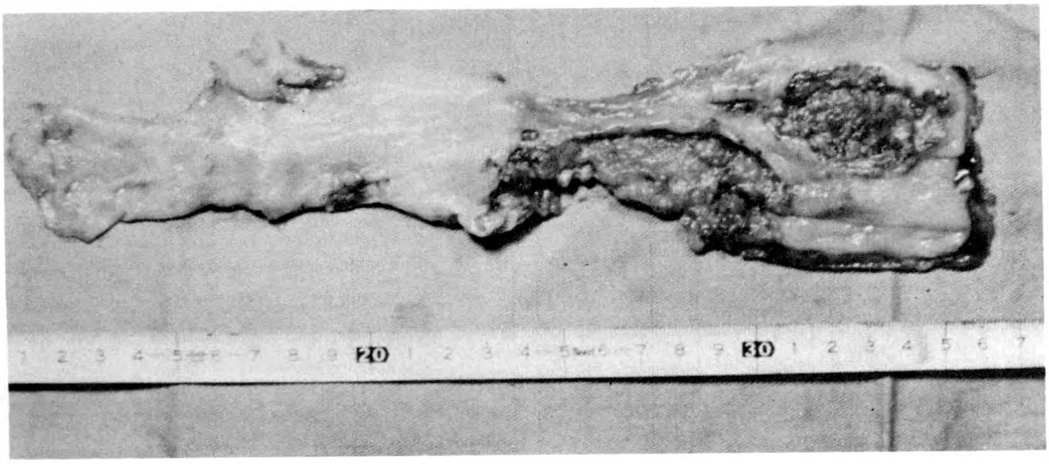

FIG. 10. Resected specimen of a giant cancer involving the entire thoracic esophagus.

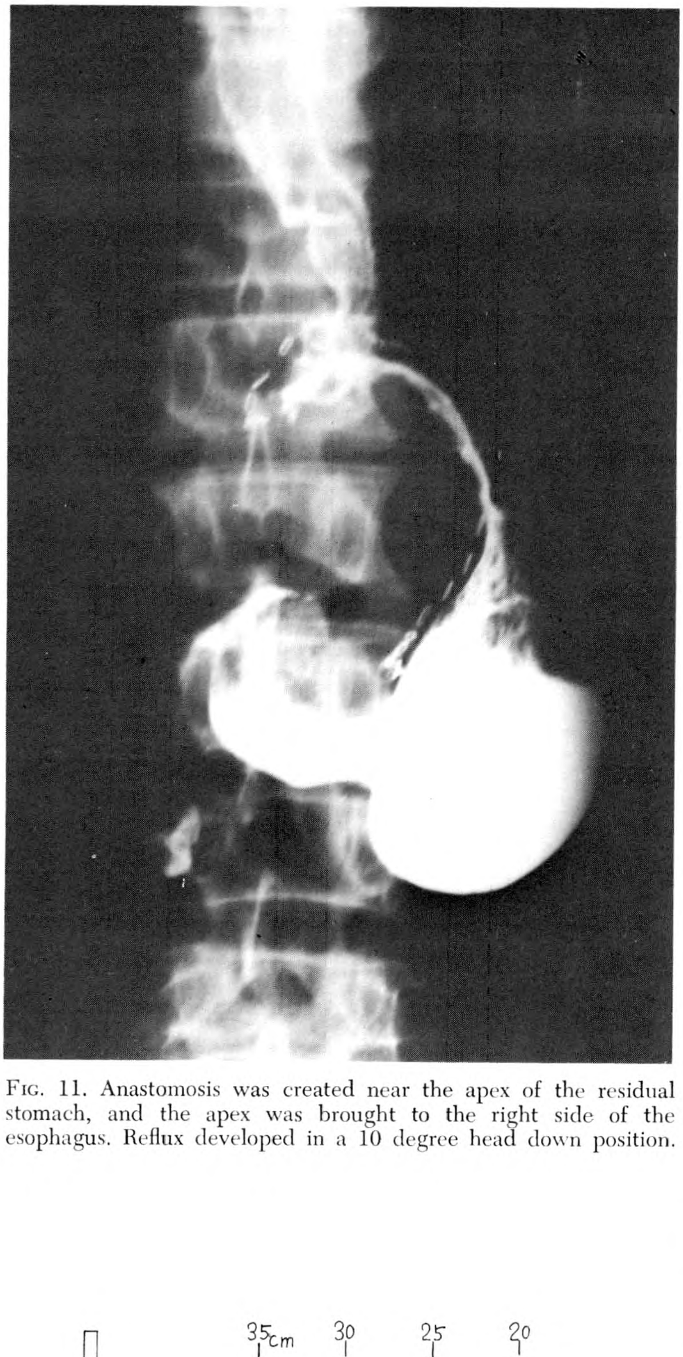

FIG. 11. Anastomosis was created near the apex of the residual stomach, and the apex was brought to the right side of the esophagus. Reflux developed in a 10 degree head down position.

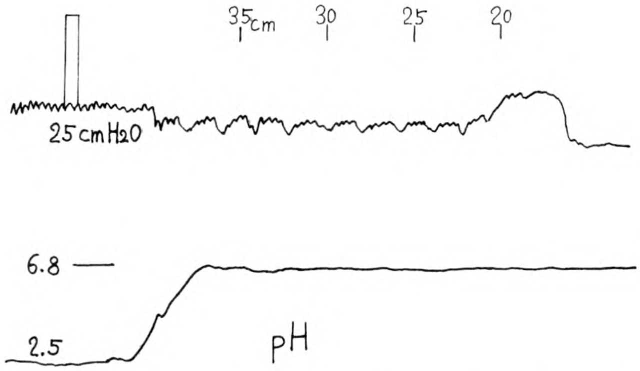

FIG. 12. Postoperative pressure and pH study don't show a zone of increased pressure and an abrupt rise in pH at the esophagogastric junction.

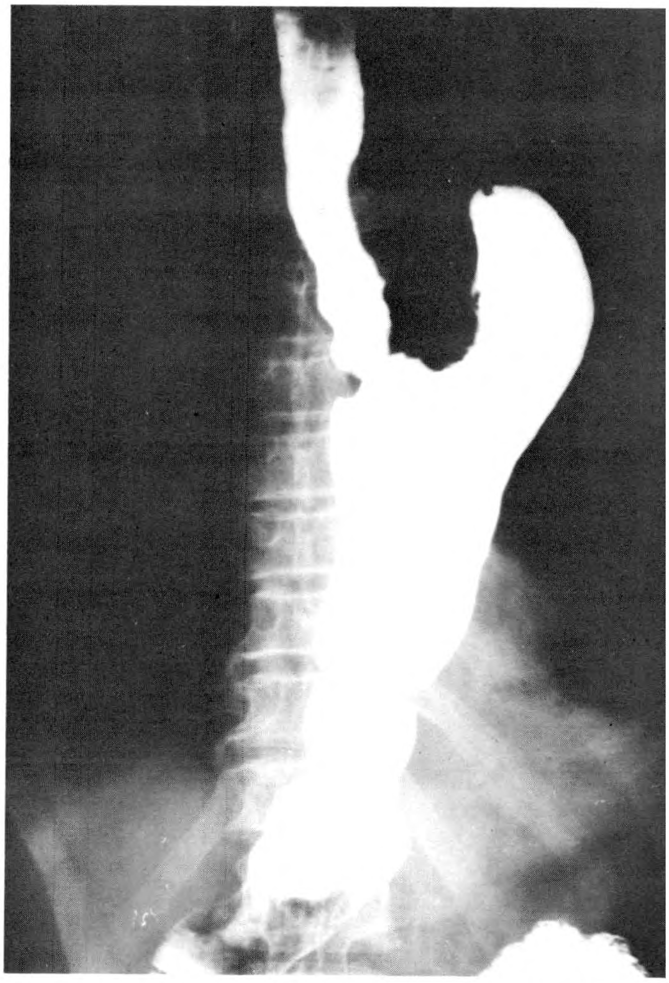

FIG. 13. Anastomosis was created at the aortic arch. Because o the presence of the aorta between the esophagus and gastric convexity, there was regurgitation of barium with the patient in hea down position.

contents. Woodward and associates[19] stated that th pyloroplasty is but an auxiliary method since the occurrence of esophagitis is incompletely prevented. Watkins,[1 Dillard,[2] and their co-workers devised a valvular esophagogastrostomy. Sirak and co-workers[15] interposed th colon, which is more resistant to digestive fluids tha the esophagus, between the proximal esophagus an the stomach. Skinner,[16] Merendino,[9] and their co-workers placed the jejunum between the esophagus an stomach. Lee[7] used the right colon with the ileoceca

TABLE 4. *Esophagogastrostomy Performed on Adult Dogs*

Group	No. of dogs
End-to-end anastomosis	5
Anterior wall anastomosis	5
Posterior wall anastomosis	5
Posterior invagination anastomosis	5
Total	20

valve as a substitute for the stomach. Pearson and associates[14] reported satisfactory results obtained with his inkwell anastomosis. In cases of diaphragmatic hernia, Baue[1] and Nissen[13] attempted to prevent reflux by carrying out plication or fundoplication.

The survey of the literature suggested that an invagination technique may also be effective in preventing reflux esophagitis in cases of esophagogastrectomy.

According to Maki,[8] the components of the physiological mechanism which prevent gastroesophageal regurgitation include: 1) the circular musculature at the lower end of the esophagus, 2) oblique muscle fibers of the stomach, 3) angle of His, 4) cardiac rosette, 5) right crus of the diaphragm, and 6) phrenicoesophageal ligament, etc.

Of these, only the angle of His is able to be recreated at esophagocardiectomy, and it was found in the present series of operations that by varying the degree of the esophagogastric angle and the length of the invaginated segment the effectiveness of the posterior in vagination anastomosis was assured. Pyloroplasty was not performed in the first fifteen cases but in the succeeding 28 cases: assessment of the result in each of all the cases was made by subjective symptoms, radiographical findings, esophageal manometry, pH recordings, and esophageal endoscopy.

Reflux esophagitis was demonstrated in 8 of 42 cases. Five cases exhibited reflux on radiographic examination; 3 developed symptomatic reflux. No reflux esophagitis occurred in cases in which the angle of His was sharp, the stomach bubble formed above the anastomosis, and the invaginated segment of the esophagus exceeded 3 cm in length, regardless of pyloroplasty.

Reflux esophagitis was exhibited radiographically in head down position in two cases in which the anastomosis was constructed at the level of the inferior margin of the aortic arch and because of the position of the aorta between the esophagus and the fundus of the stomach, the fundus was unable to exert pressure upon the esophagus.

Various techniques for esophageal reconstruction are available in instances of total thoracic esophagectomy. A right thoracotomy is most commonly used for cases with upper or middle esophageal cancer. Because change of body position during the operative procedure is time-consuming and undesirably influences circulation, esophageal resection and reconstruction without body change has been attempted in the present series in cases undergoing a left thoracolaparotomy with neck incision. Even in a case showing a giant cancerous lesion invading almost the whole segment of the thoracic esophagus, total thoracic esophagectomy and cervical esophagogastrostomy was safely performed. Except for the anastomotic method, an almost similar operative procedure was originally described by Garlock[4] and also by Sweet[17] who resected the inner half of the left clavicle and corresponding segment of the first left rib; in both descriptions the stomach lay anterior and left of the aortic arch. In the present series, the stomach was placed in the posterior mediastinum between the aortic arch and the azygos vein, preventing postoperative disturbance of pulmonary function.

The ideal technique for surgery of the esophagus combined with posterior invagination anastomosis is a one-stage operation without positional change.

Summary

Resection and reconstruction of the esophagus with a posterior invagination anastomosis was performed in 42 cases using a one-stage procedure without change of body position. Results of postoperative examinations on these patients show that by use of this technique anastomotic leak is completely prevented and the occurrence of gastroesophageal reflux markedly reduced. This technique is applicable in all cases of thoracic esophagectomy involving total resection of the thoracic esophagus.

References

1. Baue, A. E. and Belsey, R. H. R.: The Treatment of Sliding Hiatus Hernia and Reflux Esophagitis by the Mark IV Technique, Surgery, 62:396, 1967.
2. Dillard, D. H., Griffith, C. A. and Merendino, K. A.: The Surgical Construction of an Esophageal Valve to Replace the "Cardiac Sphincter." An Experimental Study, Surgical Form, 5:306, 1954.
3. Ellis, H. F., Jr. and Hood, R. T.: Experimental Esophagogastrectomy: Relation of Type of Resection to Development of Esophagitis, Surg. Gynecol. Obstet., 98:449, 1954.
4. Garlock, J. H.: Resection of Thoracic Esophagus for Gastrostomy, Surgery, 24:1, 1948.
5. Inoguchi, K. and Nakamura, T.: The Breakdown of the Suture Line in the Surgery of the Esophageal Cancer, Clinical Surgery (Japan), 20:593, 1965.
6. Katsura, S. and Abo, S.: Leakage Following Operation for Carcinoma of the Esophagus, Clinical Surgery (Japan) 20:583, 1965.
7. Lee, C. M., Jr.: Transposition of a Colon Segment as a Gastric Reservoir After Total Gastrectomy, Surg. Gynecol Obstet., 92:456, 1951.
8. Maki, T., Shiradori, T. and Okabayashi, T.: Postoperative Regressive Esophagitis, Clinical Surgery (Japan), 21:467, 1966.
9. Merendino, K. A. and Dillard, D. H.: The Concept of Sphincter Substitution by an Interposed Jejunal Segment for Anatomic and Physiologic Abnormalities at the Esophagogastric Junction, Ann. Surg., 142:486, 1955.

10. Nabeya, K.: Preoperative Examinations of Esophageal Cancer, Operation (Japan), 23:644, 1969.

11. Nakamura, Y. and Morisue, H.: On Suture Leakage Following Surgery of the Esophageal Cancer, Clinical Surgery (Japan), 20:601, 1965.

12. Nakayama, R., et al.: Investigation of Post-operative Complications of Esophageal Cancer, Operation (Japan), 24:1481, 1970.

13. Nissen, R.: Gastropexy and Fundoplication in Surgical Treatment of Hiatal Hernia, Amer. J. Dig. Dis., 6:954, 1961.

14. Pearson, F. G., Henderson, R. D. and Parrish, R. M.: An Operative Technique for the Control of Reflux Following Esophagogastrostomy, J. Thorac. Cardiovasc. Surg., 58:668, 1969.

15. Sirak, H. D., Clatworthy, H. W., Jr. and Elliott, D. W.: An Evaluation of Jejunal and Colic Transplants in Experimental Esophagitis, Surgery, 36:399, 1954.

16. Skinner, H. H. and Merendino, K. A.: An Experimen Evaluation of an Interposed Jejunal Segment Between t Esophagus and the Stomach Combined with Upper G trectomy in the Prevention of Esophagitis and Jejuni Ann. Surg., 141:201, 1955.

17. Sweet, R. H.: The Treatment of Carcinoma of the Esophag and Cardiac end of the Stomach by Surgical Extirpati Surgery, 23:952, 1948.

18. Watkins, D. H., Prevedel, A. and Harper, F. R.: A Meth of Preventing Peptic Esophagitis Following Esophagog trostomy, J. Thorac, Surg., 28:367, 1954.

19. Woodward, E. R., Thomas, H. F. and McAlhany, J. C.: Co parison of Crural Repair and Nissen Fundoplication in t Treatment of Esophageal Hiatus Hernia with Peptic E phagitis, Ann. Surg., 173:782, 1971.

20. Uchiyama, H. and Kajisa, T.: The Breakdown of the Sut Line in the Surgery of the Esophageal Cancer, Clini Surgery (Japan), 20:587, 1965.

Transthoracic Ligation Of Bleeding Esophageal Varices In Patients With Intrahepatic Portal Obstruction

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IN 1950 GEORGE CRILE described the transthoracic ligation of esophageal varices in 7 patients with extrahepatic portal blocks.[2] He recognized the superiority of portal to systemic shunts in the management of this problem, but advocated the new operation for patients who, because of previous splenectomy and portal vein thrombosis, could undergo neither a portocaval nor a splenorenal shunt. Drawing an analogy to the management of hemorrhoids, he suggested that direct obliteration of the varices might result in prolonged or even permanent control of bleeding.

In Crile's technique, the esophagus was approached through the left chest, and opened with a 2.5 cm. longitudinal incision just above the diaphragmatic hiatus. Usually 3 large columns of varices were found, and these were ligated with a running gut suture. He noted that the pliability of the mucosa enabled one to pull the veins into the small incision and ligate the varices down into the stomach and well up into the esophagus. The esophagus was closed longitudinally with an inner layer of gut and an outer layer of silk. No attempt was made to invert the edges.

Of the 7 patients followed for 6–23 months, 2 rebled. One of these had a gastric ulcer which was probably responsible for the hemorrhage. There were no operative deaths.

Crile did not claim priority for the operation when he subsequently found that Boerma[3] had reported in 1949 the direct exposure and ligation of varices in one patient. Boerma's technique consisted of longitudinal incision of the esophagus from the aortic arch to the diaphragm, multiple interruptions with suture ligatures and obliteration of the varices by injection of sclerosing solution between the points of interruption.

In 1957 Crile published a reappraisal of the transthoracic ligation of varices.[4] He theorized that although the portal hypertension secondary to portal vein thrombus might no longer exist due to the development of collateral circulation, bleeding recurred due to trauma to the large, thin-walled varices. Definitive control had been gained in 6 of 9 patients for periods of 4–9 years. He noted that the procedure carried a low mortality and morbidity in patients with a good liver reserve. All patients who had jaundice and ascites with intrahepatic blocks and hepatic decompensation died following operation, often with a fistula from failure of the esophagotomy to heal. He was discouraged about the use of the operation in these patients with cirrhosis.

Linton and Warren[6] in 1953 first reported the Massachusetts General Hospital experience with direct ligation. They suggested a somewhat different application of the operation in patients with intrahepatic blocks. It had been their observation that while patients with extrahepatic blocks bled massively and frequently, with transfusion they did not die directly as a result of hemorrhage. Conversely, half of those patients with cirrhosis died directly or indirectly from bleeding before a portosystemic shunt could be constructed. They turned to ligation as a means to control hemorrhage while the patient was being prepared for shunt surgery. In their techniques the longitudinal esophageal incision was carried down on to the stomach and closed transversely with three layers of silk. Direct healing without fistula formation was achieved in all their cases.

Nine patients with cirrhosis underwent ligation. Four rebled; 3 between 4 and 6 weeks postoperatively, and one at 5 months. One patient died in the immediate postoperative period and one 6 weeks later from liver

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failure. Seven were successfully shunted. The severity of the liver decompensation at the time of ligation was not described.

Largely as the result of the continued interest in this approach to management of bleeding varices by Robert Linton, the operation has been used rather frequently by several surgeons in the hospital during the last decade. This report will attempt to analyze its value in the management of 72 patients with portal hypertension secondary to cirrhosis, in whom it was employed during the period 1961 through 1968. Other similar patients have been managed by emergency portacaval shunts and tube tamponade. There was not general agreement among the surgeons as to the objectives and proper indications for transthoracic ligation.

Five indications determined by review of preoperative records and notes were applied. These were, first, for control of bleeding which had failed to respond to, or recurred after the use of tube tamponade in patients deemed too ill for emergency shunts. Second, to avoid the tube and its associated complications in patients too ill for an emergency shunt. Third, to make possible an elective splenorenal shunt in patients who were not controlled by more conservative measures. Fourth, failure of a shunt to control bleeding. Fifth, continued bleeding in patients in whom construction of a shunt was technically not possible. The validity of these indications is, of course, open to question, and how they should be influenced by the severity of the liver impairment was not known. The purpose of this paper is in part to delineate what, if any, are the proper indications for transthoracic ligation of varices in patients with portal hypertension secondary to an intrahepatic block.

Clinical Material

To correlate their fate after transthoracic ligation of varices with the severity of their liver disease, the patients were categorized in terms of hepatic functional reserve, after the group designation described by Child[1] (Table 1). All had intrahepatic portal blocks from either nutritional or post-neucrotic cirrhosis. Of the 72 patients coming to transthoracic ligation of esophageal varices for control of variceal hemorrhage during the 7 year period 1961 through 1968, 13 were categorized as Class A, 29 as Class B, and 30 as Class C. All bled massively, and most had an attempt at control of hemorrhage by tube tamponade. All but 7 patients received more than 4 units of blood preoperatively. In all cases the diagnosis of bleeding varices was made or strongly suspected preoperatively by upper G.I. series or endoscopy. Of those studied, 51 were males and 21 females. Forty-two patients were found to have Laennec's cirrhosis, and 30 postnecrotic cirrhosis determined either by liver biopsy at subsequent portosystemic shunt, at postmortem examination, or suggested by history. By age distribution, 4 were within the third decade, 7 in the fourth decade, 16 in the fifth decade, 24 in the sixth decade, 15 in the seventh decade, 5 in the eighth decade, and 1 patient was over 80 years of age. All patients were operated upon through a left thoracotomy, and in all but one the abdominal cavity was not entered. The esophagus was mobilized immediately above the diaphragmatic hiatus and opened through a longitudinal incision. Columns of varices were ligated with a continuous suture of chromic catgut. Closure was transverse in some and longitudinal in the others.

TABLE 1. *Clinical and Laboratory Classification of Patients With Cirrhosis in Terms of Hepatic Functional Reserve*

Group Designation	A (minimal)	B (moderate)	C (advanced)
Serum Bilirubin (mgm%)	Below 2.0	2.0–3.0	Over 3.0
Serum Albumin (gm%)	Over 3.5	3.0–3.5	Under 3.0
Ascites	None	Easily Controlled	Poorly Controlled
Neurological Disorder	None	Minimal	Advanced, "Coma"
Nutrition	Excellent	Good	Poor, "Wasting"

Results

Of 13 Class A patients studied (7 with Laennec's and 6 with postnecrotic cirrhosis,) tube tamponade was employed in 11. It was successful in 9, failed to even temporarily control bleeding in 2, and not used in 2. All but 1 patient received 5 or more units of blood preoperatively. All patients survived the operation, and none experienced recurrent hemorrhage. Eleven of the 13 came to elective portosystemic shunts. The remaining 2 were surviving at the time of this study without recurrent hemorrhage after 2 and 6 years. No esophageal fistulae developed.

Of 29 Class B patients studied (17 with Laennec's and 12 with postnecrotic cirrhosis,) tube tamponade was employed in 22. It was successful in 15, failed to control bleeding in 7, and not used in 7. All but 2 patients received 4 or more units of blood preoperatively. Nine of the 29 patients failed to survive their operation or immediate post-operative period, an operative mortality of 32%. Severe hepatic failure was present in 6 of the 9 Class B patients who died. Nine patients resumed upper G.I. bleeding within 6 weeks of their procedure, 5 coming to emergency portosystemic shunts with 80% mortality in this group. Four died without resort to further surgery. Three patients developed esophageal fistulae, and none survived this complication. The procedure was judged a success in 16 out of 29 patients, allowing these patients to come to construction of a portosystemic shunt at a time of election.

Of 30 Class C patients studied (20 with Laennec's and ten with postnecrotic cirrhosis,) tube tamponade was employed in 27. It was successful in 21, failed to even temporarily control bleeding in 6 and not used in 3. All but 2 patients received 4 or more units of blood preoperatively. Twenty-seven of the 30 patients failed to survive, a mortality of 90%. Five patients experienced recurrent gastrointestinal hemorrhage. Six patients developed esophageal fistulate. Only 3 came to an elective portosystemic shunt. Thus, the procedure could be judged successful in only 3 of 30 Class C cirrhotics.

The duration of protection from recurrence of variceal bleeding is difficult to evaluate because of the high early mortality among both Class B and Class C cirrhotics. Of the entire series, only 20 of the 72 patients had recurrence up to the time of death, shunting or time of termination of review. If one omits those patients who lived less than 2 weeks, more meaningful numbers perhaps emerge. Of this group of 20 early deaths, however, 12 had recurrence of hemorrhage and in a few it was a major factor in the fatal termination of the postoperative course.

Of the patients who lived more than 2 weeks, only 8 of 40 sustained rebleeding. Bleeding was noted in 1 patient at 3 weeks, 1 at 4 weeks, 1 at 5 weeks, 2 at 6 weeks, 1 at 8 weeks, 1 at 12 weeks and 1 at 18 weeks. Thus, there was not a time of maximum incidence of recurrence. Of 24 patients followed without shunt surgery for 6 weeks, 5 had rebled. Of 17 followed 7 weeks and longer, 3 subsequently sustained rebleeding.

Discussion

Four methods of management are commonly employed in the emergency treatment of massive upper gastrointestinal hemorrhage from esophageal varices secondary to an intrahepatic portal block. Balloon tube tamponade and administration of vasopressin, either intravenously or selectively into the superior mesenteric artery, have been generally found to be a temporary expedient, resulting in cessation of hemorrhage for a short period of time, usually hours to days.[7,8] More definitive measures have involved construction of a large portosystemic shunt utilizing the portal or superior mesenteric vein and inferior vena cava as an emergency operation. A small shunt, such as the splenorenal, has little chance of success as an emergency procedure. Directly ligating the bleeding varices, usually at the gastroesophageal junction, by the abdominal or thoracic approach is a fourth method of management. With an intrahepatic portal block this will usually control bleeding for several weeks. A large group of patients at the Massachusetts General Hospital have undergone transthoracic ligation of esophageal varices for control of hemorrhage secondary to portal hypertension from intrahepatic block. In some it was used as a means of emergency control to make possible construction of portosystemic shunt as an elective procedure, with its expected attendant lower mortality rate. In others it was used because construction of a splenorenal anastomosis was considered the procedure of choice. It also has been employed in those patients with previous extensive right upper quadrant disease processes or failed portocaval shunts. Being motivated by the lack of a previously reported large series of patients categorized in terms of hepatic functional reserve and managed in this way, we have studied this group of 72 patients in an attempt to assess this procedure's role in the management of bleeding from varices secondary to intrahepatic portal vein obstruction. In a somewhat similar series Rothwell-Jackson and Hunt[9] reported recently on 58 uncategorized cirrhotics bleeding from esophageal varices and managed by transthoracic ligation. Forty-five per cent failed to survive and 24% came to definitive shunting and survived an additional year.

The anatomic rational for direct ligation lies in the location of the collateral portal channels at the diaphragmatic hiatus. Large extramuscular channels are present on the external gastric wall below this level and on the surface of the esophagus above it. At the hiatus, however, they occupy a submucosal position and may be easily ligated intraluminally. In patients coming to postmortem in the few days following ligation, thrombus is often found in veins extending well down into the stomach and up into the esophagus, proximal and distal to segments obliterated by a running suture. Especially after use of either the Linton or Blakemore-Senkstaken tubes for control of bleeding, the esophagus is endematous and friable. Leakage from the closure was noted in 9 of 72 patients and is almost always a fatal complication in the patient with cirrhosis. The technique of closure, 2 or 3 layer, longitudinal or transverse, did not seemingly affect the incidence of leakage. Rather, it was seen with increasing frequency the more severe the liver impairment.

In Child's Class A patients, there were no deaths or leaks. Good control of bleeding resulted and all patients could have had and most did have elective shunts. In this group the indications are, first to gain control of bleeding so that an elective shunt, ordinarily a splenorenal in our hospital, may be performed. Other indications are for shunt failure or in the patient in whom emergency shunt is not possible because of technical factors.

The indications are much the same in Class B patients. The mortality was high (32%). Although bleeding was generally controlled over the short term, 5 patients eventually required emergency shunts for rebleeding before they were considered in optimal condition for an elective procedure. Ten did reach the operating table for an elective shunt and many had shown considerable improvement in liver function in the interim. Emergency shunts rather than transthoracic ligation are probably the best choice for many Class B patients. Again, it is the desire to perform a splenorenal shunt or failure or lack of feasibility of portocaval shunts that best indicate ligation.

Class C patients fared badly with ligation. It should be noted, however, that this is an especially unfavorable group since not only did they have severe and end-stage cirrhosis but also that more conservative measures had failed to control bleeding. A hoped-for result would be to obtain sufficient time to permit liver recovery prior to shunting. One-third died of liver failure after ligation. Three, however, did come to shunting and 2 of these were elective, these patients clearly having benefited from this sequence of management. The mortality rate was 90% and 20% developed esophageal leaks. In general terms, transthoracic ligation of varices offers little benefit to this group of patients. Whether emergency shunting would give better overall results is not clear.

Conclusions

1. Successful management of esophageal variceal hemorrhage due to cirrhosis by transthoracic ligation, allowing patients to come to portosystemic shunt at a time of election, directly parallels hepatic functional reserve. Good to fair hepatic function yields uniform success, whereas poor hepatic function yields results no better than emergency portosystemic decompression.

2. In the patient with previous surgery in the right upper abdomen, or a failed portosystemic shunt, transthoracic ligation of varices would appear to be an effective method of immediate management of variceal hemorrhage, allowing elective splenorenal decompression, which could not be expected to control acute hemorrhage.

3. Esophageal suture line dehiscence occurred in 12½% of those undergoing transthoracic ligation, its occurrence being confined to Child Class B and C patients.

TABLE 2. *Results of Transthoracic Ligation for Variceal Hemorrhage from Cirrhosis*

	Class A	Class B	Class C
No. Patients	13	29	30
Mortality	0 (0%)	8 (32%)	27 (90%)
Esoph. Leak	0	3	6
Later Shunt	11	15 (5 emerg)	3 (1 emerg)
Liver Failure†	0	2	10
Success*	13	14	3

* In retrospect, the operation made a significant positive contribution to the ultimate outcome and was deemed beneficial.

† Primary cause of death.

Summary

In a group of 72 patients with intrahepatic portal obstruction undergoing transthoracic ligation of esophageal varices for active hemorrhage as the immediate procedure to control bleeding, the mortality rate was 50%. The success of the procedure in controlling hemorrhage and allowing the patient to come to the definitive portosystemic shunt directly paralleled hepatic functional reserve, the procedure being uniformly successful in Child Class A patients, 55% successful in Class B patients, and only 10% successful in Class C patients. These figures are quite similar to those reported on groups undergoing emergency portocaval shunting as the definitive treatment for variceal hemorrhage and cirrhosis.[5]

In this group, balloon tamponade was employed in 58 patients and was successful in temporarily arresting hemorrhage in 43 (75%).

Nine of 72 patients (12½%) developed fistulae from the esophageal suture line. The incidence increased with increasing severity of liver decompensation and the complication was invariably fatal.

References

1. Child, C. G. 3rd: The Liver and Portal Hypertension. Philadelphia and London, W. B. Saunders Company, p. 50, 1964.
2. Crile, G. S., Jr.: Transesophageal Ligation of Bleeding Esophageal Varices. Arch. Surg., 61:654, 1950.
3. Crile, G. S., Jr.: Treatment of Esophageal Varices by Transesophageal Obliteration. Surg., Gynecol., & Obstet., 96:573, 1953.
4. Crile, G. S., Jr.: Transesophageal Ligation of Bleeding Esophageal Varices. Surgery, 42:583, 1957.
5. Edmonson, H. T., Jackson, F. C., Jules, G. L., Sigel, B. and Perrin, E. B.: Clinical Investigation Of The Portocaval Shunt, IV, A Report Of The Early Survival From The Emergency Operation. Ann. Surg., 173:372, 1971.
6. Linton, R. R. and Warren, R.: The Emergency Treatment of Massive Bleeding From Esophageal Varices By Transesophageal Suture of these Vessels at The Time of Acute Hemorrhage. Surgery, 33:243, 1953.
7. Merigan, T. C., Plotkin, G. R. and Davidson, C. S.: Effect of Intravenously Administered Posterior Pituitary Extract on Hemorrhage from Bleeding Varices. New Engl. J. Med., 266: 124, 1962.
8. Orloff, M. J.: A Comparative Study of Emergency Transesophageal Ligation and Nonsurgical Treatment of Bleeding Esophageal Varices in Unselected Patients with Cirrhosis. Surgery, 52:103, 1962.
9. Rothwell-Jackson, R. L. and Hunt, A. H.: The Results Obtained With Emergency Surgery In The Treatment Of Persistent Hemorrhage From Gastro-Esophageal Varices In The Cirrhotic Patient. Brit. J. Surg., 58:205, 1971.

Twenty-four Hour Left Ventricular Bypass in the Unanesthetized Dog:

A Study Employing Transthoracic Cannulation and a Paracorporeal Roller Pump

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DESPITE RECENT IMPROVEMENTS in the care of patients with myocardial infarction and shock, a significant number of deaths still occur. For this reason, several methods of mechanical circulatory assistance have been suggested for the treatment of refractory cardiogenic shock. Left ventricular bypass, in which blood is removed from the left atrium and pumped into the arterial system, is one such suggestion. By this method of mechanical circulatory assistance, systemic arterial blood flow and perfusion pressure increase while left atrial pressure decreases.[10,14] Moreover, myocardial oxygen consumption is reduced.[5,11]

The survival rate of dogs subjected to cardiogenic shock by coronary occlusion has been shown to be improved when left ventricular bypass was employed.[9,10,16] However, these supportive data for the beneficial effects of left ventricular bypass were obtained from experiments employing left ventricular bypass for a period of only several hours. Recent clinical evidence suggests that prolonged left ventricular bypass will be required for restoration of adequate left ventricular function following a myocardial infarction with shock.[2,3] The present study was undertaken to develop a *model* of left ventricular bypass in the canine in which the systemic and cardiac effects of long-term, temporary, mechanical circulatory assistance could be investigated.

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Methods

Fourteen adult mongrel dogs, weighing 20 to 38kg, were prepared for transthoracic left atrial cannulation (Table 1). Anesthesia was induced and maintained with sodium pentobarbital (25mg/kg). A left, fourth intercostal space thoracotomy was performed and the left atrial appendage was exposed. A woven Dacron arterial graft, 12mm in diameter, was sutured to the base of the unopened left atrial appendage (Fig. 1). Full thickness bites were taken in the atrial wall and the suture line was reinforced with felt to provide additional strength. The Dacron graft was brought from the thoracic cavity through the fourth or fifth intercostal space so the graft formed a straight line perpendicular to the plane of the lateral wall of the left atrial appendage. A polycarbonate support ring was then slid over the graft and positioned under the skin. Four sutures tacked the graft to this support ring. The chest was closed and the dog was allowed to recover. Several days later the dog was lightly anesthetized with halothane and positioned on the right side. The graft was exposed and filled with saline to displace any air. Intravenous heparin (3 mg/kg) was administered A #28 French silicon rubber mushroom cannula, held taut by a sharp stylet, was introduced through the graft and was passed into the left atrium (Fig. 2). The stylet was removed and the cannula connected to the inflow line of a small, pneumatically driven roller pump.[12] Both limbs

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[†] Fellow of the Pennsylvania Heart Association.

TABLE 1. *Transthoracic Left Atrial Cannulation* (*Preparative Phase*)

1. Anesthesia
2. Left Thoracotomy
3. Suture of Dacron Graft to Unopened Left Atrium
4. Bury end of Graft in Subcutaneous Tissue
5. Close Thoracotomy

Cannulation Phase
(24–48 Hours Later)

1. Light Anesthesia
2. Uncover End of Dacron Graft
3. Insert Left Atrial Cannula

of the divided left carotid artery were cannulated with a T-shaped, polycarbonate cannula and connected to the roller pump by a polyvinyl chloride tube, both of which had previously been treated with an antithrombogenic coating.[6] The pump was positioned in a polystyrene foam case and held to the dog's chest by a canvas restraining belt (Fig. 3). An in-line, electromagnetic flow probe was inserted in the outflow line just beyond the pump. At the end of this procedure, anesthesia was discontinued and the dog was allowed to recover.

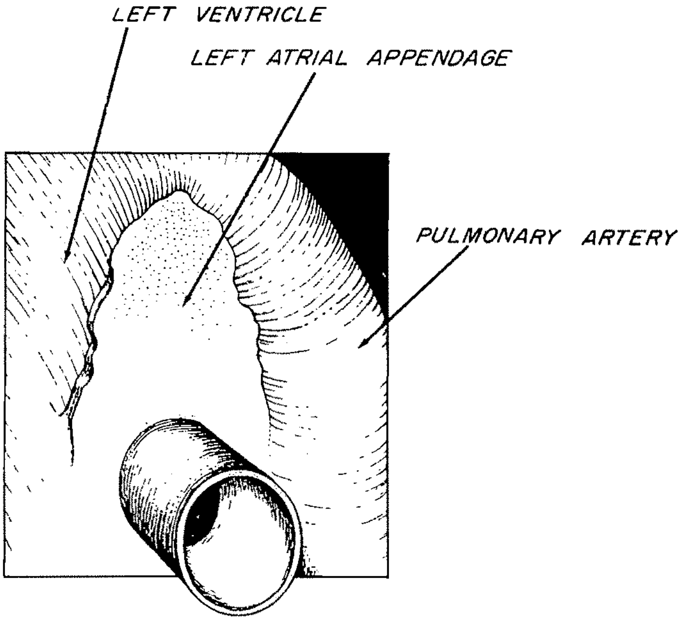

FIG. 1. The tubular Dacron graft was sutured to the base of the unopened left atrial appendage. The opposite end of the graft was brought through the rib cage and positioned beneath the skin.

Left ventricular bypass was initiated after the dog had been moved from the operating table to a supportive sling. The initial dose of heparin was succeeded by intravenous heparin, 1 mg/kg, every three hours during the entire bypass period. Five hundred to 700 ml of 5% dextrose in water were administered intravenously during the 24-hour period. No blood was transfused. Arterial blood samples were taken prior to initiation of bypass and during the bypass period for measurement of pH, pO_2, pCO_2, serum electroyltes, and plasma hemoglobin levels. The dogs breathed room air and were sedated as required. They were allowed to eat and drink. The electrocardiogram, systemic arterial pressure, and left ventricular bypass pump flow rate were continuously monitored. At the end of 24 hours of bypass, circulatory assistance was discontinued. The left atrial

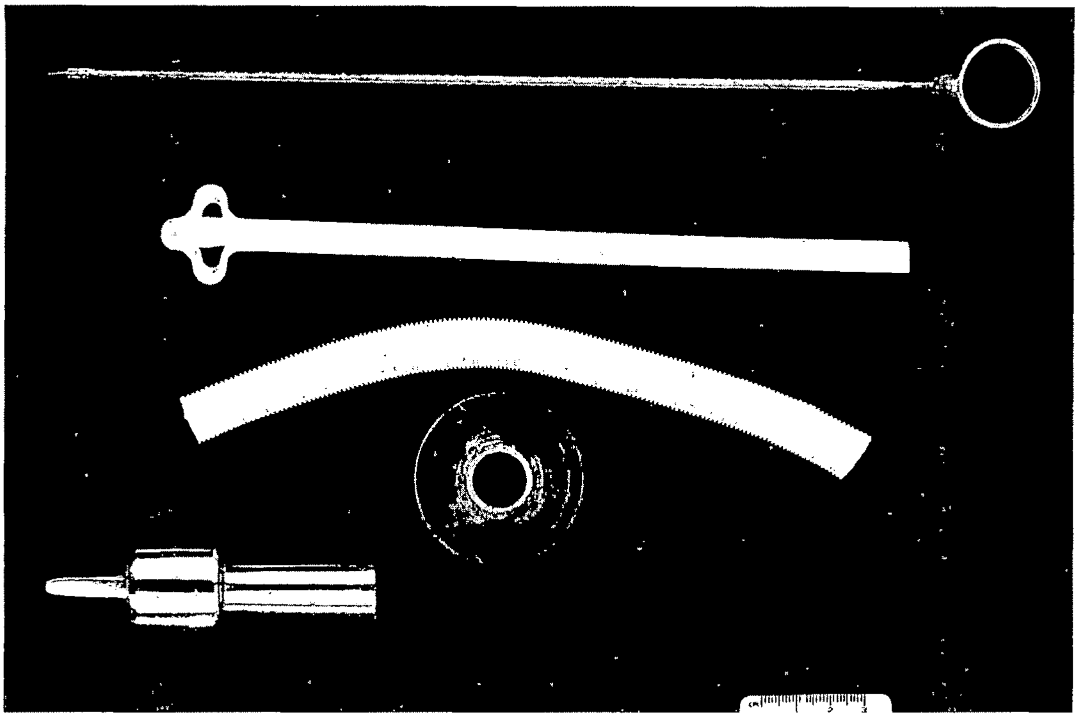

FIG. 2A. The equipment used to perform transthoracic left atrial cannulation included a steel stylet, a silicone rubber mushroom cannula (#28 French), a Dacron vascular graft (12mm), and a polycarbonate support ring. The magnified photograph of the stylet tip shows the sharp, chisel-like tip for atrial puncture and a shoulder which prevented the stylet from sliding through the cannula. See text for discussion.

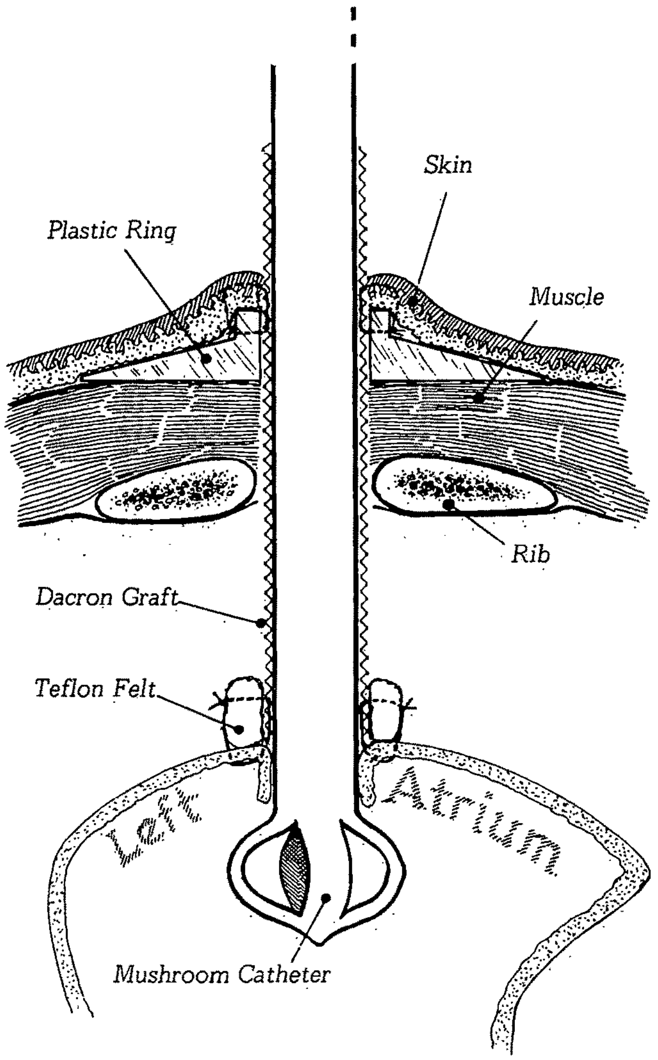

FIG. 2B. The diagramatic, cross sectional view shows the mushroom cannula in place. The polycarbonate support ring aided in fixing the Dacron graft in the proper location during cannulation. Disruption of the left atrial-graft anastomosis has not occurred when full thickness bites of atrial wall have been taken and when felt has been incorporated into the suture line.

cannula was removed during positive pressure ventilation. The skin over the Dacron graft was closed and the dog was returned to his pen. Complete autopsy was performed at the time of sacrifice one week after the termination of pumping.

Results

Ten dogs successfully underwent 24 hour left ventricular bypass. These animals were awake and were kept in a supportive sling. The flow rate of the left ventricular bypass pump averaged 34 to 105 ml/kg/minute (Table 2). The heart rate rose from 116 ± 31 (mean ± standard deviation) beats per minute prior to the onset of left ventricular bypass to 127 ± 28 beats per minute after the initiation of pumping and gradually fell to 114 ± 31 beats per minute at 24 hours (Fig. 4). These changes were not statistically significant. The systemic arterial pressure fell from a mean of 126 ± 11 mmHg, prior to the onset of left ventricular bypass, to 113 ± 8 mmHg after initiation of pumping (Fig. 4). The mean arterial pressure after 24 hours of pumping was 89 ± 19 mmHg. These changes were statistically significant ($p < 0.001$). Arterial pH, oxygen tension, and carbon dioxide tension levels determined after left ventricular bypass had been initiated were compared to those obtained after 24 hours of bypass (Fig. 5). The dogs were spontaneously breathing room air. The pH fell from 7.350 ± 0.030 to 7.328 ± 0.020; pO_2 rose from 85 ± 8 mmHg to 92 ± 13 mmHg; and the pCO_2 fell from 41 ± 5 mmHg to 39 ± 6 mmHg. These changes were not statistically significant. Serum sodium, chloride, and potassium levels remained remarkably stable during the 24 hour bypass period (Fig. 6). Plasma hemoglobin values rose from control levels of 0–2 mg/dl to between 26 and 138 mg/dl (mean 71 mg/dl) after 24 hours of left ventricular bypass (Table 2). No correlation could be detected between the left ventricular bypass pump flow rate and the plasma hemoglobin level.

The hemodynamic events that occurred during temporary stopping and reinstitution of left ventricular bypass are best illustrated by a typical example in which the left ventricular bypass pump flow rate, pulmonary artery blood flow, right ventricular stroke volume, systemic arterial pressure, and central venous pressure were monitored (Fig. 7). This awake, 23 kg dog had been on bypass for 1½ hours. The heart rate with the pump nonfunctional was 144 beats per minute which fell to 108 beats per minute when the pumping was initiated at 1.30 liters/minute. The blood pressure fell slightly from 175/112 mmHg to 160/110 mmHg. The right ventricular stroke output rose from 13.3 cc to 16.2cc but the right ventricular minute output fell slightly from 1.90 to 1.75 liters. The output of the left ventricle fell from 1.90 liters/minute to only 0.45 liters/minute with the reinstitution of bypass. In this instance, left ventricular ejection occurred only during alternate beats. The observations made in this dog were typical of those seen in the other 9 dogs during left ventricular bypass.

In each of these dogs the left atrial cannula was successfully removed after 24 hours of bypass. Autopsy examination, 1 week after termination of bypass, showed the left atrium to be free of thrombus and healing of the puncture wound site. No pneumothorax or hemothorax was present. The Dacron graft was surrounded by fibrinous material and filmy adhesions to the lungs.

One animal developed ventricular fibrillation after 9 hours of left ventricular bypass. Atuopsy demonstrated the presence of a coronary artery embolis, apparently caused by dislodgement of a thrombus from the tip of the left atrial cannula. In 3 additional instances, significant

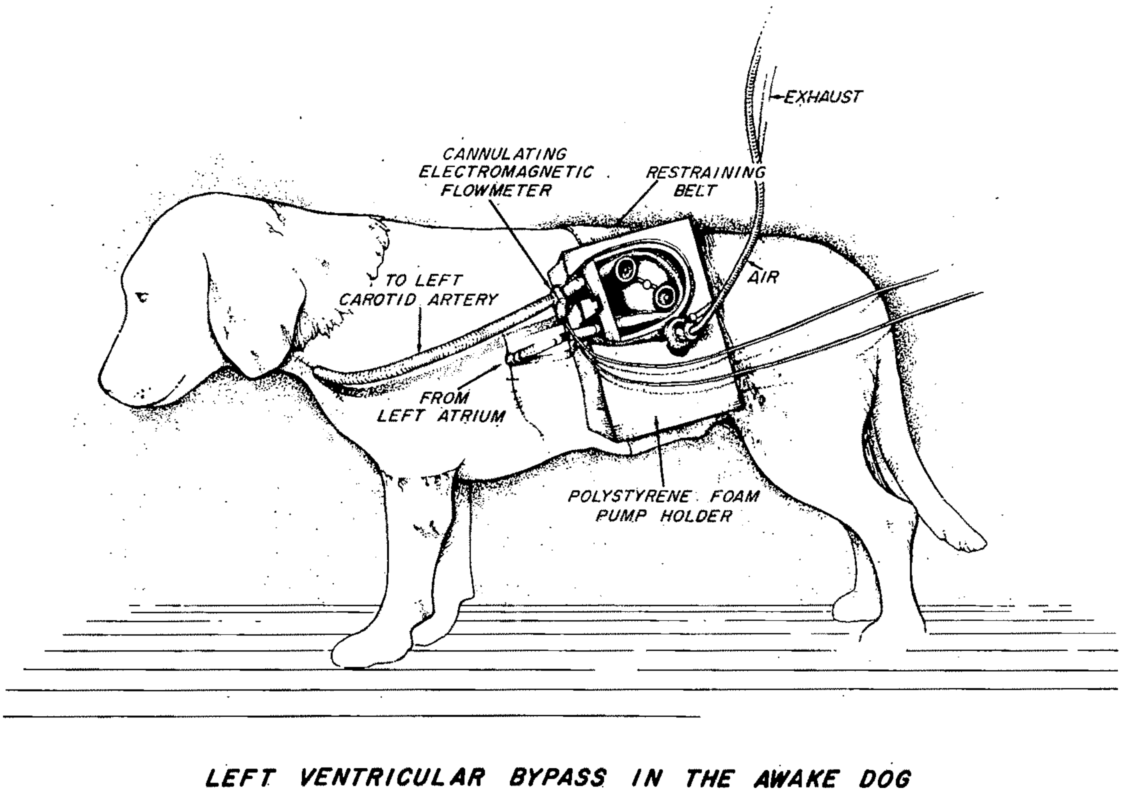
EXHAUST
CANNULATING ELECTROMAGNETIC FLOWMETER
RESTRAINING BELT
AIR
TO LEFT CAROTID ARTERY
FROM LEFT ATRIUM
POLYSTYRENE FOAM PUMP HOLDER
LEFT VENTRICULAR BYPASS IN THE AWAKE DOG

FIG. 3. The unanesthetized dogs were kept in a restraining sling during left ventricular bypass. The lightweight roller pump employed segmented polyurethane tubing and was powered by a small pneumatic motor. The pump was positioned in a polystyrene foam case and held to the dog's flank by a canvas restraining belt. The pump filled from the left atrium and discharged into both limbs of the left carotid artery by the use of a T-shaped cannula. A flowmeter was positioned in the line leading to the arterial system. The maximum output of this pump was 3 liters/minute.

TABLE 2. *Twenty-four Hour Left Ventricular Bypass in the Dog Flow Rates During Bypass and Plasma Hemoglobin Levels After Pumping*

Dog Number	30304	29736	31757	31277	31970	29724	31038	34698	34114	34582
Weight (kg)	28	31	28	38	31	27	25	23	20	22
Mean Bypass Flow Rate (ml/min)	1900	1840	1200	1280	1880	1200	2040	1380	1200	2320
Bypass Flow Rate Per Kg (ml/kg/min)	68	59	43	34	61	44	81	60	60	105
Plasma Hemoglobin (mg/dl)	113	82	36	138	77	26	31	26	92	87

intrathoracic bleeding occurred during the 24 hour period of pumping, necessitating early termination of bypass at 5, 12, and 20 hours. Autopsy, in each instance, demonstrated a hemothorax but no bleeding site could be detected.

Discussion

The development of a suitable canine model to study prolonged left ventricular bypass will permit direct application of a large body of experimental hemodynamic studies as well as techniques to produce experimental heart failure that have been performed over the years in dogs. The model we have employed has been made possible by the use of transthoracic left atrial cannulation, originally described by Rastelli and his associates,[13] and subsequently evaluated by our group for short-term (4 hour) bypass.[3] With this technique, cannulation of the left atrium by a large silicone rubber catheter has been established with reasonable technical ease and reliability. Over 50% of the cardiac output has been bypassed through

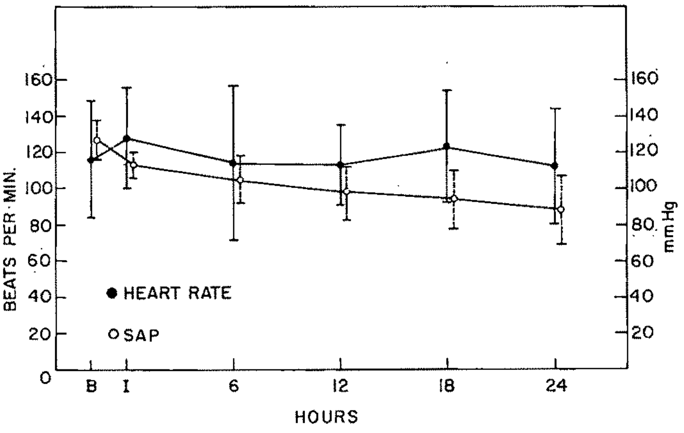

FIG. 4. Hemodynamic data during 24 hour left ventricular bypass in the awake dog. Mean heart rate and systemic arterial pressure (SAP) are indicated after induction of anesthesia but before pumping (B), just after initiation of pumping (I) and then every 6 hours thereafter. The vertical bars indicate ± one standard deviation.

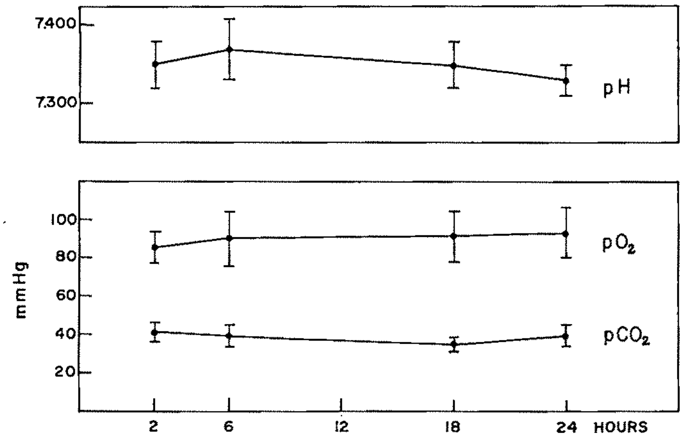

FIG. 5. Mean arterial pH and gas tensions during 24 hour left ventricular bypass. The first values were recorded at two hours after the onset of pumping at which time the dogs were awake and spontaneously breathing room air. The vertical bars indicate ± one standard deviation.

the roller pump in 7 dogs. Heart rate, blood gasses and electrolytes have remained normal during the 24 hour pumping period. The gradual fall in arterial pressure is felt to be a result of slow oozing from the operative incisions as a result of heparinization. Although all bleeding points had been carefully ligated or cauterized, blood loss of 150–250 ml from incision sites was inevitably seen. Blood transfusions were not employed.

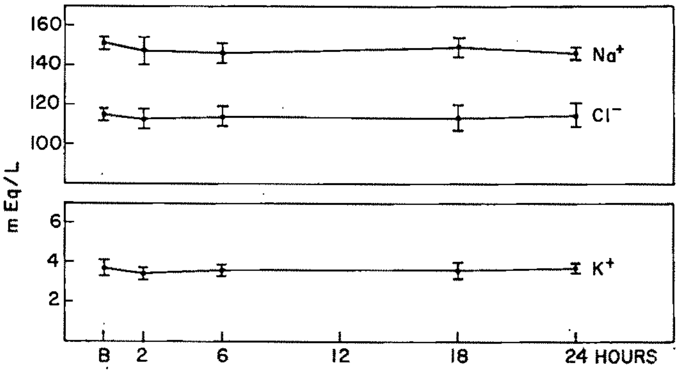

FIG. 6. Serum electrolytes during 24 hour left ventricular bypass. Mean serum sodium, chloride and potassium values are indicated after induction of anesthesia but before pumping (B), after 2 hours of bypass, after 6 hours of bypass, and every 6 hours thereafter. The vertical bars indicate ± one standard deviation.

Complications occurred in 4 animals. In one instance, inadequate anticoagulation led to thrombus formation on the left atrial cannula with subsequent coronary embolization. Three dogs developed intrathoracic bleeding during pumping. No bleeding sites could be detected. In these animals, it appeared that blood had gradually leaked from alongside the silicone rubber cannula at the left atrial puncture site, through the porous vascular graft, and into the thorax. To prevent this occurrence, the Dacron vascular graft is now lightly coated with segmented polyurethane to render it non-porous.[1]

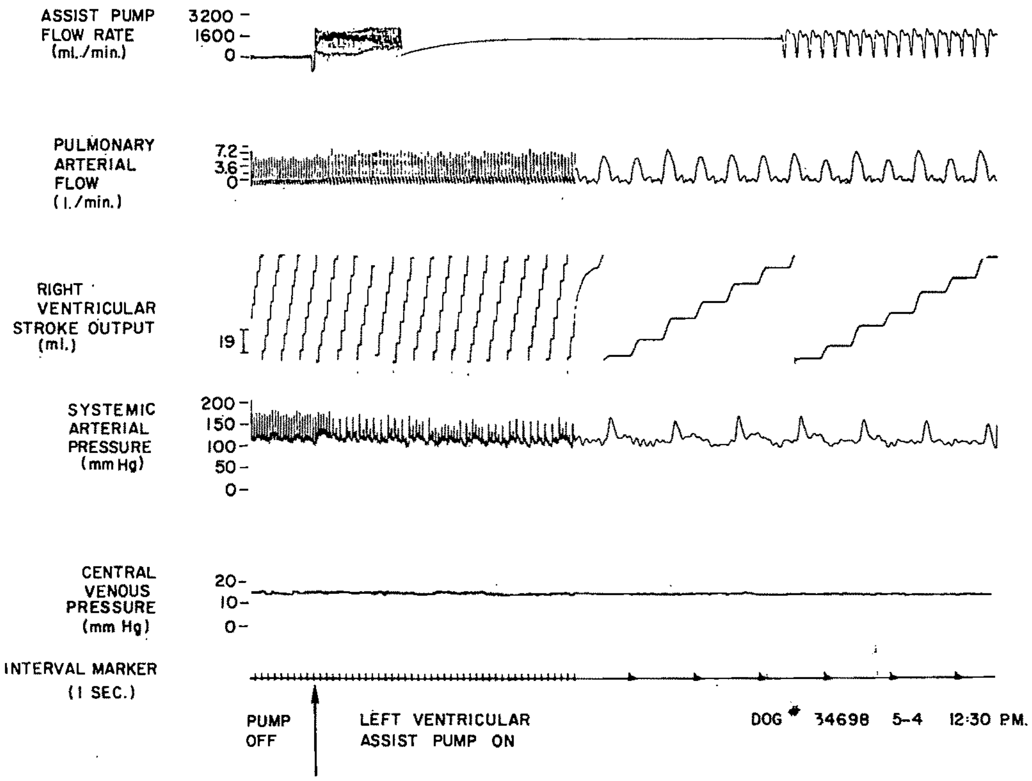

FIG. 7. Immediate hemodynamic effects of reinstituting left ventricular bypass. This awake dog had been on left ventricular bypass for 1½ hours. Pumping was discontinued and base-line values were obtained. Pumping was reinstituted at 1.3 liters/minute as indicated by the arrow. See text for discussion.

Mechanical circulatory assistance is emerging as a useful clinical tool. Proper application of the relatively noninvasive technique of intra-aortic balloon pumping in patients with refractory left ventricular failure has been life-saving to dozens of patients over the past few years.[2,7] It has also become apparent that other methods of mechanical circulatory assistance are needed which can take over a larger percentage of the left ventricular work that is possible with the intra-aortic balloon. The least invasive methods show the greatest promise as do those methods not requiring use of an oxygenator. Dennis and his associates[4] reported extensive experimental and initial clinical use of a specially designed large bore cannula which could be passed from the jugular vein into the left atrium, permitting left atrial to aortic bypass to be initiated without thoracotomy. Concern regarding the safe passage of this cannula has discouraged other investigators from developing experience with this clever technique. More recently, Zwart and his associates[16] have developed a technique of trans-arterial cannulation of the left ventricle, in which a flexible cannula is introduced from the axillary artery into the ventricle. Left ventricular to aortic bypass can thus be employed without thoracotomy. Initial clinical studies have been performed.[17]

The technique of transthoracic left atrial cannulation will permit ready access to the left atrium in patients in whom a previous thoracotomy has been performed and in whom a graft has been sewn to the unopened left atrium and positioned under the skin. This method may have particular application in certain patients with poor ventricular function who require aortocoronary bypass grafting or mitral valve replacement. In those postoperative patients in whom mechanical circulatory assistance is not required or in whom intra-aortic balloon pumping proves adequate, the graft may simply be left in place without being harmful.

Safe performance of transthoracic left atrial cannulation requires meticulous attention to detail (Table 3). A nonporous graft should be employed. The left atrial-graft suture line should be reinforced. The axis of the graft must be positioned perpendicular to the plane of the base of the left atrial appendage. A chest tube must be inserted prior to cannulation to eliminate the possibility of a pneumothorax developing and for prompt detection of intrathoracic bleeding. The graft must be kept straight during cannula insertion. The left atrial pressure should be elevated during cannula passage by maintaining an adequate fluid volume and by the use of positive pressure ventilation during the moment of cannulation. Similarly, left atrial pressure elevation during decannulation after the termination of pumping will prevent air embolis at that time.

TABLE 3. *Requirements for Safe Transthoracic Left Atrial Cannulation*

1. Non-porous graft
2. Reinforce left atrial-graft suture line
3. Insertion of chest tube prior to cannulation
4. Keep graft straight during cannula insertion
5. Maintain adequate fluid volume and positive tracheal pressure during cannulation and decannulation

This canine model of left ventricular bypass is presently being employed to evaluate extended periods of pumping and to obtain additional hemodynamic data.

Summary

Transthoracic left atrial cannulation has been used to provide a model of left atrial to aortic pumping in the dog. Ten awake, heparinized dogs have undergone 24 hour bypass successfully using a paracorporeal roller pump. Arterial pressure declined moderately while arterial pH, blood gas tensions, and serum electrolytes remained in the normal range throughout the period of bypass.

Meticulous attention must be paid to insure proper placement of the large, left atrial cannula by the transthoracic route. The method of left ventricular bypass used in this investigation may serve as a model in which the cardiac and systemic effects of long-term temporary ventricular bypass can be further studied. Clinical application of this technique may be feasible after further experience.

References

1. Boretos, J. W. and Pierce, W. S.: Segmented Polyurethane: A New Elastomer for Biomedical Applications. Science, 158:1481, 1967.
2. Buckley, M. J., Leinbach, R. C., Kastor, J. A., Laird, J. D., Kantrowitz, A. R., Madras, P. N., Sanders, C. A. and Austen, W. G.: Hemodynamic Evaluation of Intra-Aortic Balloon Pumping in Man. Circulation, 41–42:130, 1970 (Suppl. I).
3. DeBakey, M. E.: Left Ventricular Bypass Pump for Cardiac Assistance. Amer. J. Cardiol., 27:3, 1971.
4. Dennis, C., Hall, D. P., Moreno, J. R. and Senning, Å.: Left Atrial Cannulation Without Thoracotomy for Total Left Heart Bypass. Acta. Chir. Scand., 123:267, 1962.
5. Dennis, C., Hall, D. P., Moreno, J. R. and Senning, Å.: Reduction of Oxygen Utilization of the Heart by Left Heart Bypass. Circulation Res., 10:298, 1962.
6. Gott, V. L., Whiffen, J. D., Koepke, D. E., Dagget, R. L., Boake, W. C. and Young W. P.: Techniques of Applying a Graphite-Benzalconium-Heparin Coating to Various Plastics and Metals. Trans. Amer. Soc. Artif. Int. Organs., 10: 213, 1964.
7. Kantrowitz, A., Tjønneland, S., Freed, P. S., Phillips, S. J., Butner, A. N. and Sherman, J. L., Jr.: Initial Clinical Experience with Intra-Aortic Balloon Pumping in Cardiogenic Shock. J.A.M.A., 203:113, 1968.

8. Kazama, S., Chotiner, B., Metz, H. D., Lerner, E. H., Waldhausen, J. A. and Pierce, W. S.: Left Ventricular Bypass in the Dog: A Technique Employing Transthoracic Cannulation and a Paracorporeal Roller Pump. Arch. Surg., **105**:607, 1972.

9. Kennedy, J. H., Bailas, N., Hajdu, S., Beyer, A. J. and Sarap, N.: Left Heart Bypass in Left Ventricular Failure Due to Experimental Coronary Artery Ligation. J. Thorac. Cardiovasc. Surg., **51**:797, 1966.

10. MacFarlane, J. K., Scott, H. J. and Cronin, R. F. P.: Effects of Left Heart Bypass in Experimental Cardiogenic Shock. J. Thorac. Cardiovasc. Surg., **57**:214, 1969.

11. Pierce, W. S., Aaronson, A. E., Prophet, G. A., Williams, D. R. and Waldhausen, J. A.: A Comparison of Hemodynamic and Metabolic Studies During Two Types of Left Ventricular Bypass. Surg. Forum, **23**:176, 1972.

12. Pierce, W. S., Turner, M. C., Nolan, S. P. and Morrow, A. G.: The Development and Experimental Evaluation of an Implantable Left Ventricular Bypass Pump. Surgery, **66**: 1034, 1969.

13. Rastelli, G. C., Titus, J. L. and McGoon, D. C.: Transthoracic Cannulation of the Left Atrium for Circulatory Assist. J. Thorac. Cardiovasc. Surg., **56**:879, 1968.

14. Ross, J. N., Jr., Wieting, D. W., Hall, C. W., Kennedy, J. H., Gardner, H. E. and DeBakey, M. E.: Use of a Paracorporeal Left Ventricular Bypass Pump in Experimental Heart Failure. Am. J. Cardiol., **27**:12, 1971.

15. Small, M. L.: Evaluation of Left Heart Bypass in a Standardized Experimental Situation of Acute Heart Failure. J. Thorac. Cardiovasc. Surg., **54**:777, 1967.

16. Zwart, H. H. J., Kralios, A., Collan, R. and Kolff, W. J.: Transarterial Closed-Chest Left Ventricular (TaCLV) Bypass. Trans. Am. Soc. Artif. Intern. Organs, **15**:386, 1969.

17. Zwart, H. H. J., Kralios, A., Kwan-Gett, C. S., Backman, D. K., Foote, J. L., Andrade, J. D., Calton, F. M., Schoonmaker, F and Kolff, W. J.: First Clinical Application of Transarterial Closed-Chest Left Ventricular Bypass. Trans. Am. Soc. Artif. Intern. Organs, **16**:386, 1970.

Pulmonary Function After Exchange Transfusion of Stored Blood in Dogs

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THE PATHOPHYSIOLOGICAL DISTURBANCES included in the term "shock lung" have many causes. Thromboembolism has been suggested as an important etiologic factor in both animals[2,6,28] and man.[1,7,16] Stored blood contains microaggregates that are removed after passage through the pulmonary circulation.[26] It has, therefore, been hypothesized that embolic lung damage may follow massive transfusion as a result of mechanical obstruction[18] or indirectly by release of vasoactive substances[23] and/or disruption of endothelium.[3]

The present paper reports the effects of exchange transfusion of two week old ACD blood on pulmonary structure and function in dogs.

Study Outline

Two groups of 5 large (mean weight 32 ± S.E. 2.3 kg) dogs of mixed breed were maintained as blood donors. These animals were fed a high protein and iron and vitamin enriched diet. Every 2 weeks 1 group was bled, approximately 450 ml of blood from each dog was obtained in air-free plastic bags containing 75 ml of acid citrate dextrose (Fenwall blood pack). These bags were then stored at 3–4°C in a refrigerator for 2 weeks and checked for cross-match with the recipient before use.

Studies were performed in six large (mean weight 26.4 ± S.E. 1.9 kg) dogs of mixed breed.

Surgical preparation of these animals was performed under general anesthesia 2–3 days before the studies. At this time silastic catheters were sutured into a carotid and a femoral artery and a jugular vein and a Swan-Ganz, balloon tipped catheter, advanced into the pulmonary artery via the same jugular vein. The neck and groin wounds were closed with silk. These catheters were filled with dilute heparinized saline and closed with deadheads.

On the study day, general anesthesia was induced with intravenous thiopental sodium (approximately 200 mg), the trachea intubated with a cuffed tube, and anesthesia maintained with halothane (0.5–0.7% inspired concentration from Drager vaporizer) in air. Intermittent doses of succinylcholine chloride were administered intravenously to maintain relaxation during the measurement periods. The animals in the ventral position were ventilated mechanically (Bird Mark VIII assistor-controller) via a solonoid operated non-return valve. This valve ensured strict separation of inspired and expired gases.

Large constant tidal volume of ventilation was employed (mean $V_T = 26 \pm$ S.E. 2 ml/kg) and end-tidal carbon dioxide tension ($P_{ET_{CO_2}}$) of about 38 torr obtained by adjusting the inspired carbon dioxide tension ($P_{I_{CO_2}}$).

The previously placed vascular catheters were opened and the contained heparin and any clots aspirated before flushing with saline. The catheters were connected to strain gauge transducers zeroed at the mid thoracic level. The animals were not anticoagulated, damped record-

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ings were avoided by periodic small injections of saline. These pressures together with the outputs from carbon dioxide (Godart capnograph) and oxygen (Godart Rapox) analyzers and a cardiac output dye tracer (Gilson cuvette densitometer) were recorded on a Gilson polygraph.

A rectal probe was inserted and temperature maintained with a thermostatically controlled blanket.

After approximately 2 hours to achieve a steady state, control measurements (Phase 1) were performed. Pressures were recorded in the airway, aorta, superior vena cava, pulmonary artery and from the pulmonary "wedged" position. Cardiac output was measured in duplicate by dye dilution (employing 2.5 mg indocyanine green).

Respiratory volumes were measured with a dry gas meter and rate counted.

Blood and gas samples were obtained for calculation of alveolar to arterial oxygen tension difference ($P(A - a) O_2$), pulmonary venous admixture ($\dot{Q}_A/\dot{Q}_T$), anatomic (V_D/V_T Anat) and physiologic (V_D/V_T Physiol) dead space, and oxygen consumption ($\dot{V}O_2$).

Diffusing capacity (D_L) was estimated at two levels of oxygen tension to allow calculations of the capillary blood volume (V_c) components.

Inspiratory capacity (IC), functional residual capacity (FRC), total lung capacity (TLC), and airway closing volume (CV%) were measured. Finally, pulmonary extravascular water volume (PEWV) was measured.

On completion of these observations a series of blood samples were obtained for measurement of screen filtration pressure (SFP) beginning 30 minutes before starting transfusion and continuing for 2½ hours. Transfusion via a clinical filter (170 μ diameter holes) and a peripheral venous cannula was begun slowly. The stored blood was warmed to room temperature, mixed thoroughly, and a sample from each unit obtained for Sfp measurement. The estimated blood volume for the dogs was 2300 ml approximately. Five units of stored blood (total volume 2500 ml) were transfused over an hour and an equivalent volume of arterial blood removed (less some 200 ml blood to allow for blood samples).

A new steady state was achieved and some 3 hours after beginning tarnsfusion, all of the control measurements were repeated (Phase 2). The intravascular catheters were then secured, the animal allowed to recover and returned to its quarters.

The following day general anesthesia was again induced and the animal prepared as before and after a two hour stabilization period all of the measurements repeated (Phase 3).

Cardiac arrest was induced with intravenous potassium chloride, the chest opened and lungs removed. The intermediate lobe was prepared for histology and the water and blood content of the remaining lung analyzed.

Analytic Methods

Blood samples were collected in heparinized glass syringes, the dead space was flushed with blood and the samples stored in iced water before analysis.

Blood samples for measurement of oxygen and carbon dioxide tensions and pH in arterial (PaO_2, $PaCO_2$, and pH_a) and mixed venous ($P\bar{v}O_2$, $P\bar{v}CO_2$, and $pH_{\bar{v}}$) blood were analyzed with a Corning microelectrode system. Appropriate corrections were made for time and temperature differences between sampling and measurement[9,20] and systematic gas/blood factors were obtained by tonometry.

Oxygen and carbon dioxide tensions in inspired ($P_{I_{O_2}}$ and $P_{I_{CO_2}}$), mixed expired ($P_{\bar{E}_{O_2}}$ and $P_{\bar{E}_{CO_2}}$), and end-tidal ($P_{ET_{CO_2}}$) gases were analyzed and recorded continuously via the capnograph (Godart) and Rapox (Godart) analyzers. The latter instruments and the Corning microelectrode system were calibrated with gases of known composition.[19]

Oxygen content of arterial (CaO_2) and mixed venous ($C\bar{v}O_2$) blood was obtained with a carbon monoxide displacement technique,[10] and corrected for systematic differences from Van Slyke for dog blood. Our technique for measurement of carbon monoxide diffusing capacity ($D_{L_{120}}$), employing a rebreathing technique with a giant syringe, has been described previously.[8] The standard derivation of V_c from two measurements of D_L at different oxygen tensions was employed.[4]

Measurements of PEWV by double indicator dilution with I^{131} labeled albumin (RISA) and tritiated water have also been reported in detail from this laboratory.[12]

Inspiratory capacity was obtained spirometrically and FRC with a standard inert gas dilution technique. Closing volume was obtained by inflating the lung to 30 torr with oxygen and then emptying the lung at 200 ml/sec by a motor driven spirometer (Model 780 Electro-Med Instrument, Inc.). From a continuous recording of volume and nitrogen (Nitralyzer Model No. 305AR Med-Science Electronics) concentrations on an x-y plotter (Hewlett-Packard Model No. 7005B) the closing volume point was readily and repeatedly identified and the closing volume expressed as a percent of total lung volume (CV%) after correction for temperature and pressure effects.

Screen filtration pressure was determined by a modification of Swank's technique.[25] Blood samples in heparinized syringes were forced through a screen at a constant rate by a specially adapted Harvard pump and the hydrostatic pressure measured at the end of 10 seconds.

Post mortem lung blood content was estimated from the gamma emission of the I^{131} labeled albumin. The water content of the lung was obtained by weighing and drying and corrected for blood content.[13]

The bronchial tree and pulmonary artery of the intermediate lobe of lung was perfused with buffered formalin solution at 20 cm H_2O pressure for 24 hours. Histological sections were prepared for microscopy by sectioning at 6 microns. These tissues were stained with hematoxylin, eosin, PAS, Verhoeff's elastic and Masson's trichrome.

Calculations

All measured blood and gas tensions were corrected to BTPS conditions. Alveolar oxygen tension ($P_{A_{O_2}}$) was calculated from:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{\bar{E}_{CO_2}}}{PaCO_2}(P_{I_{O_2}} - P_{\bar{E}_{O_2}})$$

For calculation of $\dot{Q}_{V_A}/\dot{Q}_T\%$ the pulmonary end capillary-arterial oxygen content difference ($C\dot{c}O_2 - CaO_2$) was derived using the known alveolar and arterial PO_2 values together with the values for the P50 of the hemoglobin determined for each phase. These values were then combined with the measured arterial and venous oxygen contents:

$$\dot{Q}_{V_A}/\dot{Q}_T\% = \frac{C\dot{c}O_2 - CaO_2}{(C\dot{c}O_2 - CaO_2) + (CaO_2 - C\bar{v}O_2)} \times 100$$

assuming $PaCO_2 = P_{A_{CO_2}}$.

Physiologic dead space was calculated from:

$$\frac{V_D \text{ Physiol}}{V_T} = \frac{PaCO_2 - P_{E_{CO_2}}}{PaCO_2 - P_{I_{CO_2}}}$$

and for anatomic dead space $P_{ET_{CO_2}}$ was substituted for $PaCO_2$ in the same equation.

Pulmonary vascular resistance (PVR)

$$= \left(\frac{PAP - P \text{ wedge}}{C.O.}\right) \times 80$$

Results

The means of the measured and derived values from the six dogs are summarized in Tables 1, 2, and 3. Table 1 contains general data indicating no significant changes in temperature, Hb, $PaCO_2$, or pH, ventilation volume or rate between Phases 1, 2, and 3. Similarly, cardiac output, systemic blood pressure, central venous pressure, and pulse rate were unaltered.

Table 2 includes measurements relating to oxygen and carbon dioxide exchange. Pulmonary oxygen exchange indicated by Phase 1 PaO_2 (97 ± 2 torr), $P(A - a)O_2$ (27 ± 2 torr), and $\dot{Q}v_{A2}\dot{Q}/_T\%$ (7.0 ± 1.2%) was unchanged during Phases 2 and 3.

Pulmonary ventilatory efficiency, indicated for carbon dioxide by measurements of both physiological (Phase 1 = 31 ± 3%) and anatomic (Phase 1 = 27 ± 2%) dead spaces, was not significantly altered.

That changes in total oxygen carriage had occurred following transfusion was demonstrated by the significantly ($P < 0.05$) decreased $P\bar{v}O_2$ between Phase 1 (51 ± 2 torr) and Phase 2 (43 ± 1 torr). An extrapulmonary cause for this change was identified as a significant ($P < 0.05$) reduction of P50 from Phase 1 (30.0 ± 1.3 torr) to Phase 2 (26.6 ±0.7 torr).$C(a - \bar{v})O_2$ was constant and with a constant $C\bar{v}O_2$ in the presence of an altered hemoglobin:oxygen affinity the tissues extraction of oxygen continued at a significantly ($P < 0.05$) reduced $P\bar{v}O_2$. During Phase 3 both $P\bar{v}O_2$ (47 ± 2 torr) and P50 (27.6 ± 1.3 torr) were returning toward control levels.

TABLE 1. *General Results (Mean ±S.E. from Six Dogs*)*

	Phase 1	Phase 2	Phase 3
Temperature	37.2	36.8	38.3
°C	± 0.3	± 0.9	± 0.4
$PaCO_2$	38.7	37.9	39.7
torr	± 1.2	± 1.3	± 1.2
V_T(BTPS)	665	731	701
ml	±38	±67	±48
Respiratory Rate	7.0	7.3	7.3
/min	± 0.3	± 0.2	± 0.2
pH_a	7.367	7.4072	7.320
	± 0.103	± 0.0261	± 0.0223
Hb	12.4	13.1	11.3
g/100 ml	± 0.4	± 0.3	± 0.8
Cardiac Output	3.18	3.45	3.57
L/min	± 0.30	± 0.43	± 0.35
Systemic B. P.	122	127	108
torr	± 6	± 8	±14
Central Venous Pressure	2.6	2.9	3.1
torr	± 0.9	± 1.3	± 1.5
Pulse/min	123	141	141
	± 6	±16	±14

* No significant changes detected by analysis of variance.

Table 2, therefore, indicated no changes in pulmonary gas exchange at 3 and 24 hours after exchange transfusion.

Table 3 contains the data relating to pulmonary mechanics, hemodynamics and PEWV.

TABLE 2. *Oxygen and Carbon Dioxide Exchange (Mean ±S. E. from six Dogs)*

	Phase 1	Phase 2	Phase 3
PaO_2	97	97	97
torr	±2	±2	±2
$P(A - a)O_2$	27	26	20
torr	±2	±2	±3
$\dot{Q}_{V_A}/\dot{Q}_T$	7.0	6.05	6.7
%	±1.2	±1.0	±1.3
V_D/V_T Physiol	31	34	33
%	±3	±4	±2
V_D/V_T Anat	27	31	26
%	±2	±4	±2
$P\dot{v}_{O_2}$	51	43*	47
torr	±2	±1	±2
$C\bar{v}O_2$	12.4	12.9	10.4
torr	±1	±0.7	±1.1
$C(a - \bar{v})O_2$	4.4	4.3	4.5
ml/100 ml	±0.5	±0.4	±0.2
P50	30.0	26.6*	27.6
torr	±1.3	±0.7	±1.3

* Indicates $P < 0.05$ from analysis of variance. Only decrease $P\bar{v}O_2$ and P50 in Phase 2 compared to Phase 1 was significant.

Pulmonary artery pressure increased significantly ($P < 0.05$) from Phase 1 (12.8 ± 1.2 torr) to Phase 2 (17.3 ± 1 torr) but was within normal limits at Phase 3 (15 ± 1.2 torr). Pulmonary wedge pressure and vascular resistance were unchanged.

Pulmonary compliance, TLC, FRC, CV%, PEWV, and DL_{120} were normal throughout and V_c increased significantly from Phase 1 (66 ± 13 ml) to Phase 2 (98 ± 19 ml) and returned to normal in Phase 3 (59 ± 11 ml).

Table 3, therefore, indicates that three hours after starting transfusion (Phase 2) there was an increased pulmonary perfusion pressure and capillary blood volume, but these were not sufficient to alter other dependent measurements. Post mortem mean total lung water volume (TW) was 3.75 ± 0.33 ml/kg and the PEWV of Phase 3 as a percentage of TW was 83± 8%.

No consistent changes in lung pathology were detected at gross or microscopic examination. Occasional small subpleural hemorrhages were observed but no general emboli, hemorrhage, congestion, edema, or atelectasis.

Screen filtration pressures measured for the 30 units of dog blood after two weeks of storage had values ranging (mean 467 ± S.E. 171) from 18–>1000 mmHg, but only six units had values greater than 100 and for the remaining 24 the mean value of 54 ± S.E. 5 mmHg is only modestly increased. Normal values for SFP in fresh dog blood are 37 ± S.E. 3 mmHg in our laboratory. Samples of blood were obtained before, during, and after the exchange transfusion from both the superior vena cava proximal to the reinfusion site and from a femoral artery. Mean values for SFP obtained are shown in Table 4 and demonstrate no significant difference between venous and arterial blood and no pattern of change with time.

A transient reduction of platelet count associated with exchange transfusion is shown in Table 4. Prothrombin time and partial thromboplastin time were unchanged (Table 4) throughout, indicating no disturbance of coagulation.

Discussion

Previous investigations of hemorrhagic shock in dogs have demonstrated a redistribution of pulmonary blood flow following reinfusion of shed blood.[17,30] Three causes for this phenomenon have been considered as follows: circulating vasoactive material from ischemic tissue (in particular, products absorbed into the splanchnic circulation as a result of the characteristic hemorrhagic enteritis evinced by dogs subjected to a Wiggers type regimen); pulmonary vasoconstriction as a direct response to decreased mixed venous pH and oxygen tension; and partial obstruction of regions of the pulmonary circulation retaining particulate material contained in the reinfused blood.

In previous papers we have discussed the influence of the first two factors.[21,30] The present study is concerned with the third factor and examines the effects of massive infusions of stored blood on pulmonary function.

TABLE 3. *Pulmonary Hemodynamics, Mechanics, and Lung Water (Mean ± S. E. from Six Dogs)*

	Phase 1	Phase 2	Phase 3
Pulmonary Artery Pressure	12.8	17.3*	15.0
torr	± 1.2	± 1.0	± 1.2
Pulmonary Wedge Pressure	5.6	6.3	5.2
torr	± 0.8	± 0.8	± 1.8
Pulmonary Vascular Resistance	212	263	246
	±47	±34	±27
Total Lung Water	—	—	96
ml	—	—	± 8
Total Compliance	474	449	400
ml/cm H_2O	±40	±35	±23
TLC	3.24	3.22	3.33
BTPS L.	± 0.28	± 0.20	± 0.29
FRC	1.51	1.37	1.50
BTPS L.	± 0.23	± 0.14	± 0.21
CV%	44	49	49
	± 7	± 8	± 7
PEWV	112	98	79
ml	±15	±14	±10
$D_{L_{120}}$	25.7	24.8	22.1
ml/min/torr	± 2.1	± 2.1	± 2.5
V_c	66	98*	59
ml	±13	±19	±11

* Indicates $P < .05$ from analysis of variance. Only the increase in PAP and V_c from Phase 1 to Phase 2 was significant.

These animals were not subjected to hemorrhagic shock and, therefore, the only general disturbance present was that associated with exchange transfusion. Stored blood progressively loses 2–3 diphosphoglycerate from the red cells[24] and thus in our animals following transfusion the P50 of the hemoglobin dissociation and $P\bar{v}O_2$ were reduced. No other systemic disturbances were detected.

Pulmonary function tests were selected to examine the pulmonary hemodynamics, gas exchange, water content, and histopathology. Following transfusion of pulmonary embolism in dogs, the results of previous investigations have been variable. Some of the changes that have been demonstrated are pulmonary hemorrhages,[5] edema,[29] endothelial damage,[3] vasoconstriction,[23] increases in dead space,[11] pulmonary vascular resistance,[15] pulmonary artery pressure,[15] functional residual capacity[15] and diffusing capacity,[15] and a reduction of compliance. Tests for these aspects were, therefore, included.

Our animals received an exchange transfusion of two week old blood in a volume exceeding their estimated total blood volume. Our battery of tests revealed that this resulted in no impairment of gas exchange as evidenced by PaO_2, $P(A - a)O_2$, $\dot{Q}_{VA}/\dot{Q}_T\%$ and $\dot{V}_D/\dot{V}_T$; no change in pulmonary mechanics revealed by total compliance, TLC, FRC, and CV% (the latter being a test of small airway mechanics); maintenance of normal distribution of pulmonary blood flow shown by D_LCO_{120} and PEWV; no evidence of interstitial pulmonary edema by

TABLE 4. *Hematologic Data (Mean ± Standard Error From Six Dogs)*

	Pre-Infusion	Post-Infusion Min 15	30	60	120
Screen Filtration Pressure, torr	37 ± 3	35 ± 2	35 ± 2	40 ± 3	43 ± 2
Prothrombin Time, sec	8.0 ± 0.3	8.0 ± 0.3	8.2 ± 0.5	8.0 ± 0.4	9.4 ± 0.3
Partial Thromboplastin Time, sec	17 ± 1	19 ± 4	17 ± 1	16 ± 1	17 ± 1
Platelets, thousands/cm^3	71 ± 13	40* ± 5	41* ± 7	52 ± 15	80 ± 13

* Indicates post-infusion different from pre-infusion value by analysis of variance with $P < 0.05$.

microscopy, total lung water or PEWV and no consistent macroscopic or microscopic pathological findings.

The only significant alterations were modest increases in V_c and pulmonary artery pressure immediately following transfusion. Both of these effects probably resulted from some pulmonary obstruction but they had returned to normal by 24 hours and no emboli were seen by microscopy at that time.

In general, these findings agree with previous reports that following modest pulmonary embolism changes are minimal and pulmonary artery pressure often the only parameter altered and then only transiently.[14]

Previous reports of microaggregate formation in stored blood[17,22] and the associated increase in SFP[25,27] had led us to expect that our animals would be exposed to relatively massive embolism. The lung has been identified as the site of deposition of such microaggregates following intravenous infusion and we, therefore, expected substantial deterioration of pulmonary function.

The former premise was incorrect, a significant increase in SFP at two weeks did not occur in much of the stored blood and following transfusion did not alter the whole animal SFP to any extent. Thus, with only one unit in five containing many microaggregates it is not surprising that the observed pulmonary changes were minor.

The difference between these findings of minimal SFP changes in stored blood is at variance with the reports of others suggesting consistent and uniform increases but probably represents the effects of species and time variables that have not yet been adequately evaluated. These findings are to some extent reassuring in that not all stored blood has an increased SFP and the lung is well suited to continue normal function when presented with a reasonable embolic load. They also provide a partial explanation for apparent inconsistencies in the literature when transfusion has had variable effects on lung function but comparison of the microaggregate content of the infusate has not been made.

The clinical relevance of these findings deserves comment. If human blood behaves like dog blood with regard to the variability of microaggregate formation and SFP changes, then large volumes of transfused blood would produce lung function changes only if coincidentally most of the units have increased SFP's. Convincing evidence of pulmonary microembolism has been demonstrated in man following cardiopulmonary bypass,[7] trauma,[16] and shock states. It seems probable that in these conditions infusion of microaggregates is combined with other factors to induce lung damage. Transfusion of microembolic must be regarded as a stress that can be avoided by employing an in-line micro filter.

Summary

Whole blood obtained from donor dogs was stored in sterile ACD bags for 2 weeks. Six recipient dogs were subjected to an exchange transfusion exceeding their total blood volume.

Pulmonary function tests including measurement of gas exchange, venous admixture, mechanics, blood flow distribution, and water volume were performed before and at 3 and 24 hours after exchange transfusion. Gross and microscopic examination of the lungs was undertaken following sacrifice of the animals. The only pulmonary abnormalities detected were a small increase of pulmonary artery pressure and capillary blood volume 3 hours after transfusion. Screen filtration pressure measurments of the infused blood after two weeks of storage were performed to assess microaggregate formation and were found to be considerably increased in only 6 of the 30 units of blood used.

The following conclusions are suggested:

1. Storage of dog blood is not necessarily associated with formation of microaggregates or dramatic increase in SFP.
2. Massive transfusion of such stored blood is not accompanied by significant changes in pulmonary function in otherwise healthy dogs.
3. The minor changes of P50, $P\bar{v}O_2$, pulmonary artery pressure, and capillary blood volume detected in these studies may assume more importance when combined with other stress factors such as are associated with traumatic and septic shock states.

References

1. Blaisdell, F. W., Lim, R. C., Amberg, J. R., Choy, S. H., Hall, A. D. and Thomas, A. N.: Pulmonary Microembolism. Arch. Surg., 93:776, 1966.
2. Blaisdell, F. W., Lim, R. C., Jr. and Stallone, R. J.: The Mechanism of Pulmonary Damage Following Traumatic Shock. Surg. Gynec. Obstet., 130:15, 1970.

3. Connell, R. S. and Swank, R. L.: Pulmonary Fine Structure after Hemorrhagic Shock and Transfusion of Aging Blood. Sixth European Conference on Microcirculation, Aalborg, 1970. J. Ditzel, editor. Baste, S. Karger Press.
4. Forster, R. E.: Diffusion of Gases. Handbook of Physiology, section 3, vol. I, Respiration. W. O. Fenn and H. Rahn editors. Washington, D.C., American Physiological Society, p. 839, 1964.
5. Henry, J. N., McArdle, A. H., Scott, H. J. and Gurd, F. N.: A Study of the Acute and Chronic Respiratory Pathophysiology of Hemorrhagic Shock. J. Thor. Cardiovasc. Surg., **54**:666, 1967.
6. Hissen, W. and Swank, R. L.: Screen Filtration Pressure and Pulmonary Hypertension. Am. J. Physiol., **209**:715, 1965.
7. Jenevein, E. P. and Weiss, D. L.: Platelet Microemboli Associated with Massive Blood Transfusion. Am. J. Path., **45**:313, 1964.
8. Kallos, T. and Smith, T. C.: Measurement of the Pulmonary Diffusing Capacity in Anesthetized Man. Abstracts of Scientific Papers, American Society of Anesthesiologists Annual Meeting, p. 73, 1969.
9. Kelman, G. R. and Nunn, J. F.: Nomograms for Correction of Blood PO_2, PCO_2, pH, and Base Excess for Time and Temperature. J. Appl. Physiol., **21**:1484, 1966.
10. Klingenmaier, C. H., Behar, M. G. and Smith, T. C.: Blood Oxygen Content Measured by Oxygen Tension after Release by Carbon Monoxide. J. Appl. Physiol., **26**:653, 1969.
11. Levy, S. E., Stein, M., Totten, R. S., Bruderman, I., Wessler, S. and Robin, E. D.: Ventilation-perfusion Abnormalities in Experimental Pulmonary Embolism. J. Clin. Invest., **44**:1699, 1965.
12. Marshall, B. E. and Wyche, M. Q.: Pulmonary Extravascular Water Volume During Halothane-Oxygen Anesthesia in Dogs. Anesthesiology, **32**:530, 1970.
13. Marshall, B. E.: Determination of the Blood Content of Lungs in vitro. J. Appl. Physiol., **31**:643, 1971.
14. Marshall, R. and Allison, P. R.: Pulmonary Embolism by Small Blood Clots. Thorax, **17**:289, 1962.
15. Marshall, R. and Dunnill, M. S.: Experimental Pulmonary Embolism by Platelet Agglutinates in Dogs. Thorax, **21**:372, 1966.
16. Moseley, R. V. and Doty, D. B.: Death Associated with Multiple Pulmonary Emboli Soon after Battle Injury. Ann. Surg., **171**:336, 1970.
17. Naimark, A., Dugard, A. and Rangno, R. E.: Regional Pulmonary Blood Flow and Gas Exchange in Hemorrhagic Shock. J. Appl. Physiol., **25**:301, 1968.
18. Robb, H. J.: Microembolism in the Pathophysiology of Shock. Angiology, **16**:405, 1965.
19. Scholander, P. F.: Analyzer for Accurate Estimation of Respiratory Gases in One-half Cubic Centimeter Samples. J. Biol. Chem., **167**:235, 1947.
20. Severinghaus, J. W.: Blood Gas Calculator. J. Appl. Physiol., **21**:1108, 1966.
21. Soma, L. R., Neufeld, G. R., Dodd, D. L. and Marshall, B. E.: Physiological and Physiological Aspects of Hemorrhagic Shock in the Canine Lung. J. Appl. Physiol., submitted for publication, 1972.
22. Solis, R. T. and Gibbs, M. B.: Filtration of the Microaggregates in Stored Blood. Transfusion, **12**:245, 1972.
23. Stein, M. and Thomas, D. P.: Role of Platelets in the Acute Pulmonary Responses to Endotoxin. J. Appl. Physiol., **23**:47, 1967.
24. Sugerman, H. J., Davidson, D., Vibul, S., Delivoria-Papadopoulos, M., Miller, L. and Oski, F.: The Basis of Defective Oxygen Delivery from Stored Blood. Surg. Gynec. Obstet., **131**:733, 1970.
25. Swank, R. L.: Alteration of Blood on Storage: Measurement of Adhesiveness of "Aging" Platelets and Leukocytes and Their Removal by Filtration. New Engl. J. Med., **265**:728, 1961.
26. Swank, R. L. and Porter, G. A.: Disappearance of Microemboli Transfused into Patients During Cardiopulmonary Bypass. Transfusion, **3**:192, 1963.
27. Swank, R. L. and Edwards, M. J.: Microvascular Occlusion by Platelet Emboli after Transfusion and Shock. Microvasc. Res., **1**:15, 1968.
28. Swank, R. L.: Platelet Aggregation: Its Role and Cause in Surgical Shock. J. Trauma, **8**:872, 1968.
29. Wilson, J. W., Ratliff, N. B., Hackel, D. B. and Martin, A. M.: The Lung in Hemorrhagic Shock. Am. J. Path., **58**:337, 1970.
30. Wyche, M. Q. and Marshall, B. E.: Lung Function, Pulmonary Extravascular Water Volume and Hemodynamics in Early Hemorrhagic Shock in Anesthetized Dogs. Ann. Surg., **174**:296, 1971.

Effect of Platelet Inhibition on Platelet Phenomena in Cardiopulmonary Bypass in Pigs

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Clinical cardiopulmonary bypass (CPB) has long been associated with a decrease in platelet count. The loss of platelets is independent of the type of oxygenator prime and exceeds that expected from hemodilution alone.[9,13] The cause of this loss of platelets has usually been assumed to be trauma in the blood oxygenator which activates platelets to produce platelet microthrombi. This loss of platelets is of more than academic interest since the thrombocytopenia contributes to the hemostatic defect following surgery and several of the complications of cardiopulmonary bypass, including depression of renal, pulmonary, neurologic and cardiac function, have been ascribed to microembolization by platelet aggregates.

The present study was undertaken to determine the effects of a known inhibitor of platelet function, dipyridamole (Persantine^R),* on platelet count and function, and sequellae of microembolization during CPB in pigs. Serial measurements of platelet count, hematocrit and ADP induced platelet aggregation were made, and blood flow and blood gases were measured at specified times on bypass in order to estimate the adequacy of perfusion. Lung, heart and kidney biopsies were taken at the conclusion of bypass.

Materials and Methods

Techniques of Anesthesia and Surgery

Techniques of anesthesia were designed to allow minimum use of drugs. The details of these techniques will be published separately.[3] Briefly stated, 21–25 kg. pigs were sedated with a short-acting barbiturate† administered through an ear vein, intubated and maintained with a N_2O-O_2 curare regimen. Central venous blood samples were obtained from catheters fed via the external jugular vein.

Cardiopulmonary Bypass

The mediastinum was exposed through a bilateral thoracotomy in the second intercostal space. Following heparinization (3 mg/kg), bypass was instituted in the usual fashion after cannulation of the ascending aorta through the brachiocephalic artery and inferior vena cava (IVC) via the right atrial appendage. The superior vena cava was drained via side holes in the IVC cannula. In all instances, the oxygenator‡ was primed with 1500 cc. lactated Ringer's solution containing 20 m.Eq. KCl and 89.2 m.Eq. $NaHCO_3$. No blood or any other solution was used in the prime or at any other time during bypass. Venous blood was drained by gravity and arterial blood returned with a Sarns roller pump,§ oxygen was delivered to the oxygenator at 4 L/min.

Blood Sampling

Venous blood samples prior to CPB were taken from the central venous catheter. Venous blood samples on bypass were obtained through the venous port in the oxygenator. All arterial samples were obtained by needle puncture of

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* Persantine^R, supplied by Dr. G. H. Worsley, Boehringer-Ingelheim.

† Pentothal^R, Abbott Laboratories.

‡ Temptrol^R, Pediatric Q-110, Bentley Laboratories.

§ Sarns Inc., Ann Arbor, Michigan.

the ascending aorta. Simultaneous arterial and venous samples were taken at all times. There was never any significant difference in the results of platelet studies between arterial or venous blood for any of the tests and these values were therefore averaged in the results given.

Platelet Counts

Platelet counts were determined by the method of Brecher and Cronkite.[4]

ADP Induced Platelet Aggregation

Nine cc. of whole blood was added to one cc. of 3.8% sodium citrate. Platelet-rich-plasma (PRP) was prepared by low-speed centrifugation (0 setting*) for 45 minutes; following removal of the PRP, platelet-poor-plasma (PPP) was prepared by highspeed (30 setting) centrifugation for 10 minutes. Platelet count of PRP was normalized to 200,000 by addition of PPP when necessary. ADP† (0.05 cc. of 10^{-2} *M*) was added to 0.5 cc. PRP and the changes in light transmission recorded on a recorder‡ connected to a Payton aggregation module.§ The module was standardized so that PPP represented maximal light transmission and PRP, minimal transmission.

Blood Gases

pO_2, pCO_2, pH, O_2 saturation, and HCO_3^- were measured according to standard methods with a pH/gas analyser.‖

Blood Flow on Bypass

Blood flow was measured by calibration of the roller pump. No attempt was made to manipulate the flow into more acceptable ranges by use of drugs, additional fluid, etc. Blood flow, therefore, depended solely on venous return.

Histology

Biopsies from the right upper lobe of the lung, apex of the heart, and kidney were removed immediately at termination of bypass, fixed in 10% formalin, and stained with hematoxylin and eosin (H&E), periodic-acid-Schiff (PAS) and phosphotungstic acid hemotoxylin (PTAH) after appropriate processing.

Control vs. Experimental Animals

In experimental animals, dipyridamole (10 mg/kg body weight) was added to the pump prime. Otherwise all techniques in the control and experimental animals were the same. There were 9 animals in each group.

Statistical Analyses

Mean values for control and experimental animals were compared by means of the unpaired two-sample t test. Deviations from unity for certain values were determined by the one-sample t test.

Results

All results are expressed as the mean of 9 control or 9 experimental animals, ± one standard deviation unless otherwise stated. The values for hematocrit, platelet count, ADP-induced aggregation (AIA), and blood gases are the means of simultaneous arterial and venous samples. There was no significant difference in mean weight, hematocrit, platelet count or AIA prior to CPB between the control and Persantine animals.

Hematocrit and Platelet Counts

In Table 1, serial measurements of hematocrit are shown. It can be noted that the bloodless pump prime causes a hemodilution of about 50% in both control and experimental animals, this effect being somewhat greater in the first 10 minutes of CPB. At all times during CPB, hemodilution was slightly greater in the Persantine animals, probably due to the vasodilating effect of Persantine, causing expansion of the intravascular space at the expense of extravascular fluid. These differences were statistically significant only at 60 minutes of CPB ($p < .05$).

In Table 2, serial measurements of platelet counts are shown. It can be seen that platelet counts in control animals have fallen precipitously by 30 minutes of CPB and the effect is even more pronounced by 60 minutes. In Persantine animals, platelet counts are maintained throughout the 60 minutes of CPB.

In Table 3, the effect of hemodilution on platelet count is taken into account. Using hematocrit to estimate hemodilution, the ratio of platelet count (% of pre-CPB) to hematocrit (% of pre-CPB) is indicated. A ratio of 1.00 would indicate that the drop in platelet count was no greater than that expected from dilution alone. The ratio at all times during CPB in Persantine animals does not differ significantly from unity and this is true also for

TABLE 1. *Hematocrit (Hct), as a Percentage of Pre-CPB Values, as a Function of Time on CPB.*

Time (Mins.)	Control Hct	Persantine Hct
5	45.4% ± 9.9	40.0% ± 6.3
10	48.0% ± 8.1	41.6% ± 5.6
30	51.0% ± 7.0	45.4% ± 5.6
60	51.6% ± 5.6	46.5% ± 4.4

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* L-708 Combination Centrifuge, Phillips-Drucker, Astoria, Oregon.

† Sigma Chemical, St. Louis, Mo.

‡ Westronics, Model D-11A, Fort Worth, Tex.

§ Payton Ass., Scarborough, Ontario.

‖ Instrumentation Laboratories, Boston, Mass.

TABLE 2. *Platelet Counts, as a Percentage of Pre-CPB Values, as a Function of Time on CPB.*

Time (Mins.)	Control Platelet Count	Persantine Platelet Count
5	50.5% ± 7.7	40.0% ± 9.0
10	46.4% ± 6.0	43.7% ± 7.2
30	31.5% ± 8.0	46.3% ± 12.8
60	27.7% ± 9.3	48.2% ± 16.9

control animals at 5 and 10 minutes ($p > .10$ for all values). However in control animals at 30 and 60 minutes, the ratios indicate that platelet counts have dropped much more than expected from dilution alone ($p < .01$ for both values). These results are depicted graphically in Fig. 1.

In sum, these values indicate that, as in man, absolute platelet counts drop considerably during CPB in the pig and this decrease can be prevented by the presence of Persantine in the pump prime.

ADP-Induced Aggregation

In Table 4, it is shown that AIA falls during the course of CPB in both sets of animals and the decrease is greater in control than in experimental animals. This difference is significant at 60 minutes ($p < .01$). A graph depicts the results for all animals in Fig. 2. Typical curves in a control animal are shown in Fig. 4.

These platelet function studies indicate that platelets remaining at the termination of CPB are relatively nonreactive in control animals. AIA does not depend on platelet count since the aggregometer is balanced in such a way as to negate any differences in platelet count. We confirmed this by studying AIA on PRP of platelet counts from 80–400,000, prepared by dilution with PPP. The AIA did not change regardless of platelet count in this range. Therefore, platelet function following CPB was depressed independently of thrombocytopenia.

Blood Gases

In general, blood gases indicated better perfusion in Persantine than in control animals. The mean venous pH at 30 minutes in control animals was 7.14 (S.D. = ±.04) while in Persantine animals, the mean pH was 7.23 (±.11).

TABLE 3. *Ratios of Platelet Counts (Percentage of Pre-CPB Values) to Hematocrits (Percentage of Pre-CPB) as a Function of Time on CPB.*

Time (Mins.)	Control Ratio Platelet Count : Hct	Persantine Ratio Platelet Count : Hct
5	1.14 ± .24	1.01 ± .26
10	.98 ± .12	1.06 ± .19
30	.63 ± .21	1.08 ± .29
60	.55 ± .24	1.03 ± .29

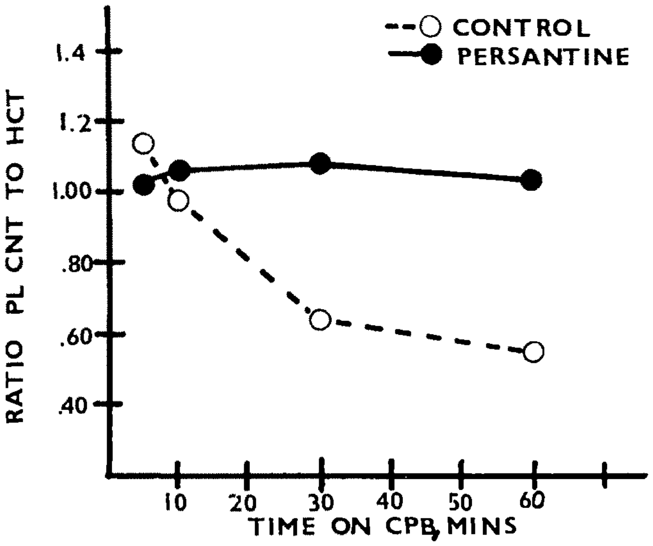


FIG. 1. Ratio platelet count (percentage of pre-CPB values) to hematocrit (percentage of pre-CPB values) and time on CPB. Ratios less than 1.00 indicate loss of platelets greater than expected from hemodilution alone.

Blood Flow

In the first 15–20 minutes of CPB, flows were approximately equal in both groups. Thereafter, a progressive drop in flow was noted in both groups, this drop being much greater in control animals. At 60 minutes of CPB, mean flow was 17.8 (±4.2) cc/min/kg in control animals, and 36.9 (±10.4) cc/min/kg in Persantine animals. This difference is highly significant ($p < .01$).

The blood gases and blood flows suggest that Persantine allows better perfusion of the microcirculation since flow was strictly a function of venous return.

It is possible that the increase in flow in Persantine animals was due to its vasodilating effect, apart from any effect on microthrombosis. In 5 additional animals, CPB was instituted and Persantine administered at 50 minutes of CPB when the effects on microthrombosis would be expected to be minimal, since most platelets would already have disappeared. In these animals, the mean increase in flow 20 minutes after administration of Persantine was insignificant (3 cc/min/kg) suggesting that the major portion of the increased flow in Persantine animals was not due to vasodilation.

TABLE 4. *ADP-induced Platelet Aggregation (AIA), as a Percentage of Pre-CPB Values, as a Function of Time on CPB. (AIA was Determined from the Maximal Slopes of the Curves.)*

Time (Mins.)	Control AIA	Persantine AIA
5	50.0% ± 16.5	56.9% ± 12.9
10	65.2% ± 29.5	61.4% ± 17.0
30	54.6% ± 41.0	68.5% ± 17.6
60	34.8% ± 20.4	63.1% ± 18.2

Furthermore, it was noted that, in the Persantine group, those animals which sustained the greatest drop in platelet count generally had the lowest flow rates. Fig. 3 shows the relationship between flow rate and maintenance of platelet counts; the correlation coefficient is .91 ($p < .01$).

These results suggest that the improved microcirculatory perfusion in Persantine animals is a result of decreased microthrombosis and/or microembolization.

Pathology

PTAH stains were generally unrewarding, as might be expected, since heparinized animals cannot readily form fibrin. PAS stains likewise showed no more abnormalities than could be noted on ordinary H & E stains. There was little difference in pathology between the 2 groups. Microthrombi probably would have had little time to become fixed in the tissues in the short bypass performed. While there appeared to be more microthrombosis in control animals, this was not generally great enough to allow objective grading.

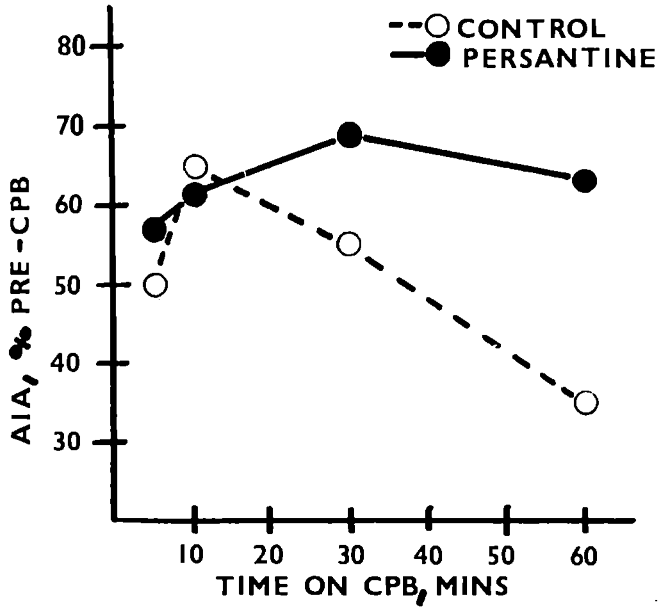


FIG. 2. ADP-induced platelet aggregation (as a percentage of pre-CPB values) as a function of time on CPB.

Discussion

While the loss of platelets during CPB has long been recognized, its significance has not been understood or agreed upon. The accumulated evidence of the past several years favours the hypothesis that platelets are activated in the extracorporeal system by contact with the foreign surface or by ADP released from hemolyzed red cells. Activated platelets clump together to form microthrombi which are then infused into the patient and lodge in the capillary beds of the various organs, producing varying degrees of intra- or postoperative dysfunction.

Microparticles have been demonstrated to emanate from the oxygenator by several techniques[1,10,21,23] and have been implicated in the pathogenesis of cerebral,[17] pulmonary,[1] renal[1] and cardiac[16] lesions following CPB. Filtration of the infused arterial blood has been shown to reduce neurologic deficit both in animals[17] and man.[6]

In the present experiment, the loss of platelets during CPB in the absence of blood prime was demonstrated. This loss of platelets was largely prevented by the use of Persantine in the oxygenator prime. In this acute experiment, organ function was not tested and pathologic studies were unrewarding. Nevertheless, as platelet loss seems related to microthrombosis and microthrombosis related to organ function, it would appear that the use of dipyridamole would allow improved post-CPB organ function.

Flow on CPB and Microthrombosis

In the present experiment in which flow was accepted "as is" without attempted manipulation, there was evidence that flow was inversely related to the degree of microthrombosis:

1. Initial flow rates were equal in both control and experimental animals and flow rates started decreasing at about the time platelet loss began.
2. Flow in Persantine animals was directly related to the degree to which platelets were retained (Fig. 3).
3. Persantine led to minimal increase in flow when given after 50 minutes of CPB when the major amount of microthrombosis was completed.

Other experiments support the thesis that flow on CPB is related to the degree of platelet microthrombosis. Ashmore *et al.*[2] were able to approximately double flow rates by filtration of blood leaving the oxygenator to remove

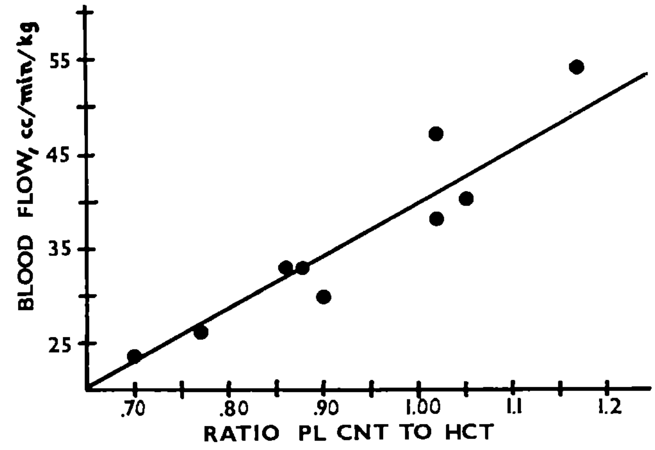
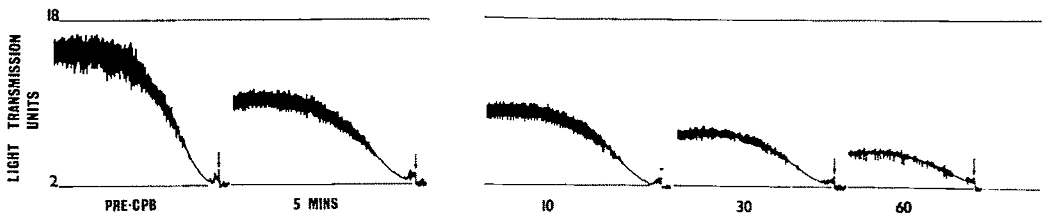


FIG. 3. Maximum obtainable blood flow at 60 minutes of CPB in Persantine animals as a function of the degree to which platelets were preserved, expressed as the ratio of platelet count (percentage of pre-CPB) to hematocrit (percentage of pre-CPB) at 60 minutes. There is good correlation between flow and the degree of platelet preservation ($R = .91$).

FIG. 4. Typical curves of ADP-induced platelet aggregation as a function of time on CPB in a control animal. The arrow indicates the point at which ADP was added.



microthrombi. Rittenhouse *et al.*[18] demonstrated improved flows when Persantine was added to the prime in an isolated lung preparation. Thus, removal or prevention of microthrombi might be expected to allow for a smoother intra-operative course on CPB.

Thrombocytopathy and the Postoperative Bleeding Diathesis

In the present experiments, a late bypass thrombocytopathy has been demonstrated. This finding is not surprising in view of several experiments demonstrating that in the normal animal there is a distribution of circulating platelets ranging from the young, large platelets which are more active (and reactive) to the old, small and less active platelets.[7,8,19] One would therefore postulate that the most reactive platelets are activated during CPB, forming microthrombi and disappearing from the circulation. Less reactive platelets, less susceptible to activation during CPB, remain in the circulation but their relatively poor quality renders them less effective in hemostasis. In a continuing study, we have demonstrated such a thrombocytopathy (by the ADP-induced aggregation test) post-CPB in man.

These findings indicate that, in the study of post-CPB bleeding problems, emphasis should be placed on the possibility of poorly functioning platelets regardless of the platelet count which may be near normal. Since platelets are the first line of defence in the coagulation sequence, poor platelet function may be a major contributor to the post-CPB bleeding diathesis. Although not generally appreciated, others have also noted a post-CPB qualitative platelet defect.[13,20]

Platelet function was more well preserved in Persantine animals since the more reactive platelets were inhibited from forming microthrombi. Loss of some function (AIA 63.1% of pre-CPB values at 60 mins.) indicates that the most reactive platelets are removed but, since platelet counts are maintained, they are probably replaced by others from the marrow and spleen. In man, the bulk of loss of platelets occurs in the first few minutes of CPB following which an equilibrium between destruction and production is probably established.[9] Some residual effect of Persantine may also be reflected in the depressed platelet function tests; ordinarily, Persantine rapidly (within 30-60 mins.) enters the enterohepatic circulation[14] but its metabolism on CPB has not been studied.

Prospects for Clinical Use of Persantine

It is inferred from the present experiment and from the others cited, that dipyridamole might offer the following advantages if used in CPB: 1) smoother intraoperative course with more facile maintenance of flow; 2) smoother postoperative course with improved neurologic, pulmonary, renal function; 3) improved post-CPB platelet function and less hemorrhagic diathesis.

Small oral doses of dipyridamole given to prevent emboli from artificial valves[6,22] or microthrombosis in renal transplants or glomerulonephritis[11,12] have been generally well tolerated; gastrointestinal side effects have occurred but possibly no more frequently than in patients taking placebos.[22] The limiting factor in IV doses has been hypotension, secondary to vasodilation. Experimentally, this hypotension is short-lived, even with massive doses, and would appear to be of little consequence in CPB when flow, not pressure, is the important parameter. Other possible toxic effects of massive doses are unknown.

Persantine disappears from the circulation largely by entering the enterohepatic circulation whence it is excreted into the feces.[14] The possibility of altered metabolism on CPB must be borne in mind. Further experiments in our laboratory indicate that platelet counts cannot be maintained for two hours with the single dose (in the oxygenator prime) of dipyridamole. Clinical use would therefore often require repeat doses, raising the questions of possible additive toxicity or tachyphylaxis, although there is no evidence for this.[15]

In our planning for this experiment, the question was raised whether the combination of heparin and dipyridamole would lead to a massive and uncontrollable hemorrhagic diathesis. This was not noted in our acute experiments and since platelet function was more well preserved in Persantine animals, seems unlikely.

A major problem in clinical extension of our findings is that controlled studies of the effects of the drug are very difficult since the use of bank blood makes data interpretation less than perfect and the complications we are concerned with (neurologic, pulmonary, hemorrhagic, etc.) require subjective evaluations, have other possible contributing etiologies, and are of such an incidence that a great number of patients would have to be studied.

There is presently no known contraindication to the use of massive doses of Persantine in CPB. Side effects are present with the use of any drug and undoubtedly would become apparent with the routine use of Persantine.

Many inhibitors of platelet function are available, however, and some of these undoubtedly would perform as well as Persantine in CPB. The present experiment indicates that a well designed, controlled clinical trial of a platelet inhibitor in CPB is warranted.

Summary

The effect of dipyridamole, a potent platelet inhibitor, on platelet-related phenomena in cardiopulmonary bypass (CPB) was studied in pigs. No blood was used in the oxygenator prime. In control animals, absolute platelet counts and platelet function were depressed following CPB. In dipyridamole animals, platelet counts were maintained and platelet function, although depressed, was much improved over that in control animals. Mean flow in dipyridamole animals was over twice that in controls. It is concluded that the use of a platelet inhibitor in CPB might offer the following advantages: 1) increased platelet numbers; 2) improved platelet function; 3) more facile maintenance of flow on CPB; 4) improved post-CPB organ function.

References

1. Allardyce, D. B., Yoshida, S. H. and Ashmore, P. G.: The Importance of Microembolism in the Pathogenesis of Organ Dysfunction Caused by Prolonged Use of the Pump Oxygenator. J. Thorac. Cardiovasc. Surg., **52**:706, 1966.
2. Ashmore P. G., Swank, R. L., Gallery, R., Ambrose, P. and Prichard, K. H.: Effect of Dacron Wool Filtration on the Microembolic Phenomenon in Extracorporeal Circulation. J. Thorac. Cardiovasc. Surg., **63**:240, 1972.
3. Becker, R. M., Lord, L. and Dobell, A. R. C.: Techniques and Pitfalls of Anesthesia and Thoracic Surgery in the Pig. J. Surg. Res. **13**:215, 1972.
4. Brecher, G. and Cronkite, E.: Morphology and Enumeration of Blood Platelets. J. Appl. Physiol. **3**:365, 1950.
5. Harker, L. A. and Slichter, S. J.: Studies of Platelet and Fibrinogen Kinetics in Patients with Prosthetic Heart Valves. New Engl. J. Med. **283**:302, 1970.
6. Hill, J. D., Osborn, J. J., Swank, R. L., Aguilar, M. J., de Lanerolle, P. and Gerbode, F.: Experience Using a New Dacron Wool Filter During Extracorporeal Circulation. Arch. Surg., **101**:649, 1970.
7. Karpatkin, S.: Heterogeneity of Human Platelets; Metabolic and Kinetic Evidence Suggestive of Young and Old Platelets. Series Haematol., **4**:75, 1971.
8. Karpatkin, S.: Heterogeneity of Human Platelets. II. Functional Evidence of Young and Old Platelets. J. Clin. Invest., **48**:1083, 1969.
9. Kendall, A. G. and Lowenstein, L.: Alterations in Blood Coagulation and Hemostasis During Extracorporeal Circulation. Canad. Med. Ass. J., **87**:786, 1962.
10. Kessler, J. and Patterson, R. H.: The Production of Microemboli by Various Blood Oxygenators. Ann. Thorac. Surg., **9**:221, 1970.
11. Kincaid-Smith, P.: The Pathogenesis of the Vascular and Glomerular Lesions of Rejection in Renal Allografts and Their Modification by Antithrombotic and Anticoagulant Drugs. Australas. Ann. Med., **19**:201, 1970.
12. Kincaid-Smith, P., Saker, B. M. and Fairley, K. F.: Anticoagulants in "Irreversible" Acute Renal Failure. Lancet, **2**:1360, 1968.
13. McKenzie, F. N., Dhall, D. P., Arfors, K. E., Nordlund, S. and Matheson, N. A.: Blood Platelet Behaviour During and After Open Heart Surgery. Brit. Med. J., **2**:795, 1969.
14. Mellinger, T. J. and Bohorfoush, J. C.: Paths and Tissue Distribution of Dipyridamole (Persantine). Arch. Int. Pharmacodyn., **156**:380, 1965.
15. Mellinger, T. J. and Bohorfoush, J. C.: Blood Levels of Dipyridamole (Persantine) in Humans. Arch Int. Pharmacodyn., **163**:471, 1966.
16. Najafi, H., Henson, D., Dye, W., Javid, H., Hunter, J., Callaghan, R., Eisenstein, R. and Julian, O. C.: Left Ventricular Hemorrhagic Necrosis. Ann. Thorac. Surg., **7**:550, 1969.
17. Patterson, R. H., Kessler, J. and Bergland, R. M.: A Filter to Prevent Cerebral Damage During Experimental Cardiopulmonary Bypass. Surg. Gynec. Obstet., **132**:71, 1971.
18. Rittenhouse, E. A., Hessel, E. A., Ito, C. S. and Merendino, K. A.: Effect of Dipyridamole on Microaggregate Formation in the Pump Oxygenator. Ann. Surg., **175**:1, 1972.
19. Sahud, M. A.: Platelet Size and Number in Alcoholic Thrombocytopenia. New Engl. J. Med., **286**:355, 1972.
20. Signori, E. E., Penner, J. A. and Kahn, D. R.: Coagulation Defects and Bleeding in Open Heart Surgery. Ann. Thorac. Surg., **8**:521, 1969.
21. Simmons, E., MaGuire, C., Lichti, E., Helvey, W. and Almond, C.: A Comparison of the Microparticles Produced when Two Disposible Bag Oxygenators and a Disc Oxygenator Are Used for Cardiopulmonary Bypass. J. Thorac. Cardiovasc. Surg., **63**:613, 1972.
22. Sullivan, J. M., Harken, D. E. and Gorlin, R.: Pharmacologic Control of Thromboembolic Complications of Cardiac Valve Replacement. New Engl. J. Med., **284**:1391, 1971.
23. Swank, R. L., Hirsch, H., Breuer, M. and Hissen, W.: Effect of Glass Wool Filtration on Blood During Extracorporeal Circulation. Surg. Gynec. Obstet., **117**:547, 1963.

Plasma Levels of Elastase, Trypsin and Their Inhibitors in Bile Induced Pancreatitis in the Dog

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IN 1968, GEOKAS AND ASSOCIATES measured elastase in pancreatic tissue in acute pancreatitis induced by the intraductal injection of bile,[7] trypsin[8] and elastase[9] in dogs. They measured elastase activity in pancreatic tissue and suggested a key role for elastase in producing elastolysis, destruction of vessel walls, thrombosis and intestinal hemorrhage. The vascular injury that accompanies bile induced acute pancreatitis in dogs was attributed to the release of intrapancreatic elastase as evidenced by a decrease in proelastase content per gram of necrotic pancreatic tissue and by the histological evidence of elastolysis.

Studies in this laboratory have demonstrated that the pancreatic secretion of elastase parallels that of amylase, lipase and trypsinogen under secretin and pancreozymin-secretin stimulation. At the same time, elastase inhibitors in pancreatic juice and normal plasma were demonstrated.[16] Several investigators have previously reported the presence of elastase inhibitors in serum[6,20] and in pancreatic extract. Rinderknecht[15] and Satake, *et al.*[17] have recently observed a decrease in plasma elastolytic activity in patients with acute pancreatitis.

Fabiani[6] also reported an early significant rise in elastase inhibitor level in serum in patients with acute pancreatitis, although the elastase inhibitor levels found in patients with chronic pancreatitis or pancreatic carcinoma was not significantly different from that of normal patients.

The current experiments were designed to study the elastase activity and their inhibitors in the plasma and lymph of dogs following the induction of pancreatitis by the injection of bile into the pancreatic duct. Plasma, amylase, lipase, trypsin, and trypsinogen levels were monitored simultaneously as were lymph amylase levels.

Materials and Methods

Fifteen mongrel dogs of both sexes (15–20 kg/body weight) were anesthetized with sodium pentobarbital. Pancreatitis was induced by the injection of autologeous bile (0.5 ml/kg) into the pancreatic duct under approximately 10 cm of water pressure. The portal vein, left thoracic lymph duct and femoral vein were exposed and cannulated for repetitive sampling. Heparinized blood samples were drawn from each site before the injection of bile, then hourly for 3 hours and at the fifth hour. Lymph was collected from the thoracic duct cannula continuously for 10 minutes during each of the above periods. After the collection of each 10 minute lymph sample, lymph flow was returned to the jugular vein by means of the thoracic duct cannula. A total of 21 pancreatic tissue biopsies for total elastase assay and for histological examination were taken from 7 pancreatitis dogs at the end of the 5 hours of study. In addition, 9 pancreatic biopsies for assay of total elastase content were taken from 3 normal dogs. Normal pancreatic juice was collected for the assay of elastase inhibitor from 11 dogs, having chronically implanted Thomas pancreatic cannulae, under constant stimulation with pancreozymin and secretin. The method of collection of pancreatic juice has been described previously.[3]

Plasma, lymph and tissue elastase levels were measured according to the fluorometric method of Rinderknecht,[15]

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using an elastin dimethylaminoaphatalene sulfonic acid (elastin-DNS) substrate. *Total elastase* activity was measured after activation for proelastase by adding 4 mg trypsin (2X cryst. salt free, lypholized, Sigma, Co., St. Louis, Mo.). *Free elastase* activity was measured without activation of proelastase. The elastase results are reported as micrograms of elastase per milliliter of plasma or pancreatic juice, or milligram of wet tissue, based on standard porcine elastase (Sigma Co., 75 units/mg).

Elastase inhibitor levels were measured as the percentage decrease of recovery of a known amount of elastolytic activity, after adding plasma or pancreatic juice. The elastolytic activity of 1 μg and 2 μg of twice-crystallized porcine pancreatic elastase (Sigma Co., 75 units/mg) on 45 mg elastin-DNS substrate was determined in three series of duplicate tubes, designated A, B, and C. The A series, which was used as a standard, contained the enzyme substrate mixture, with bicine buffer, pH 8.8, in a total volume of 5 ml. The B series contained the enzyme-substrate, 0.2 ml pancreatic juice or plasma and bicine buffer, in a total volume of 5 ml. The C series contained the same amount of substrate without the enzyme, in the same total volume, with 0.2 ml pancreatic juice or plasma. The degree of inhibition was calculated against the standard and expressed as a percentage: $\{A - (B - C)/A + C\} \times 100$

Amylase determinations were made according to the method of Somogyi,[19] lipase by the Cherry-Crandall method[11] and trypsin and trypsinogen[5] using benzoylarginyl-paranitroanilide as the substrate. Histological examination of the pancreas was done after standard preparation utilizing hemotoxylin-eosin stains. Results are reported as means with standard error of the mean.

Results

The plasma amylase and lipase levels following injection of the bile are shown in Table 1. The mean plasma amylase levels increased to 286% of control value within one hour after induction of pancreatitis and remained high for the 5 hours of study, having risen rapidly following the pancreatic insult. Thoracic lymph amylase concentrations were higher than those of plasma. Lymphatic flow was almost constant, ranging between 0.8 to 1.0 ml/min. with a mean of 0.87 (±0.3 ml/min). The changes in lipase levels paralleled those observed for amylase. In each animal the lipase activity also rose within the first hour and remained high throughout the 5 hour period.

The changes in trypsinogen and trypsin levels observed in plasma and thoracic duct lymph are shown in Table 2. Trypsinogen levels increased within 1 hour after bile injection and remained high throughout the study. The thoracic lymph trypsinogen concentration was higher than that of plasma during the control period and after the induction of pancreatitis, especially during the 3–5 hour interval. The changes in trypsin levels in plasma and lymph, however, were not as pronounced as those of amylase, lipase and trypsinogen. The concentrations of trypsin and trypsinogen in the blood and thoracic duct lymph showed more variation both in the control periods and after pancreatitis, but after 5 hours were found to have become elevated in the plasma in most experiments (Table 2).

The measurement of trypsin inhibitor capacity, in peripheral and portal plasma and in the thoracic duct lymph are shown in Table 3. Trypsin inhibitor capacity did not change significantly following induction of pancreatitis although it tended to drop in the portal vein.

Table 4 shows the results of measurements of free and total elastase in the plasma and thoracic duct lymph. In contrast to trypsin and trypsinogen, the total elastase levels decreased at all sites of sampling. The fall was progressive throughout the five hour period. The concentration of free elastase in the plasma increased slightly during the first hour following the induction of

TABLE 1. *Amylcse and Lipase Levels in Plasma and Amylase Levels in Thoracic Duct Lymph*

	Femoral Vein		Thoracic Duct Lymph	Portal Vein	
Duration of Pancreatitis	Amylase	Lipase	Amylase	Amylase	Lipase
Controls	5,530	1.5	7,075	6,280	1.7
	± 830		± 770	±1,075	±0.2
One Hour	15,832	4.7	20,482	15,850	5.0
	±2,491	±0.4	±3,350	±2,579	±0.7
Two Hours	18,980	4.6	31,641	19,850	4.9
	±2,491	±0.6	±6,530	±2,579	±0.3
Three Hours	18,415	3.2	34,641	21,550	4.5
	±3,456	±0.6	±6,530	±3,492	±0.9
Five Hours	18,583	—	43,500	23,550	—
	±3,456		±2,170	±4,699	

Amylase Levels: Somogyi units per 100 ml ± S. E. mean.
Lipase Levels: Cherry-Crandall unit per ml ± S. E. mean.

TABLE 2. *Trypsinogen and Trypsin Level (units/ml ± S. E. mean) in Plasma and Lymph*

	Femoral Vein		Thoracic Duct Lymph		Portal Vein	
Duration of Pancreatitis	Trypsinogen	Trypsin	Trypsinogen	Trypsin	Trypsinogen	Trypsin
Control	1.7 ±0.2	2.2 ±0.5	5.0 ±2.0	6.9 ±2.0	2.7 ±0.3	2.7 ±0.7
One Hour	4.0 ±0.6	4.0 ±0.6	9.8 ±3.0	5.0 ±1.6	4.2 ±0.9	3.9 ±0.6
Two Hours	4.8 ±0.6	4.1 ±0.3	9.1 ±2.0	6.7 ±1.8	6.0 ±0.8	4.7 ±0.9
Three Hours	6.2 ±0.9	4.3 ±0.9	13.8 ±3.0	4.0 ±1.8	6.4 ±0.7	5.2 ±0.2
Five Hours	6.5 ±0.8	5.3 ±0.9	12.1 ±1.1	7.1 ±1.8	6.5 ±0.8	7.6 ±0.9

pancreatitis. Subsequently it decreased slightly. The level of free elastase in lymph remained stable for three hours but then decreased slightly.

The changes in elastase inhibitor capacity observed in the plasma and lymph after the induction of pancreatitis are shown in Table 5. The elastase inhibitor capacity dropped slightly in the femoral vein but showed no consistent change in the thoracic duct following induction of pancreatitis. The portal vein elastase inhibitor capacity, however, appeared to increase slightly after pancreatitis.

The total elastase activity, observed in pancreatic tissue, before and after induction of pancreatitis is shown in Table 6. Elastase activity decreased 31% in the head, 51% in the body and 54% in the tail of the pancreas within five hours after the onset of pancreatitis.

Elastase inhibitor capacity in eleven specimens of normal pancreatic juice, ranged from 38% to 62% with a mean of 50% (±2.2% S.E.) (Table 7).

Discussion

The changes in plasma and lymph amylase and lipase activity following the bile induced pancreatitis in this series of experiments were similar to that reported by previous investigators.[4,10] Few investigators have been concerned with the changes in circulating trypsin following the induction of pancreatitis because trypsin inhibitor[2,12] interferes with the determination of serum trypsin levels. The findings in the present investigation, however, are consistent with the findings of Nardi and Lee.[13] Following pancreatitis the trypsin levels showed little change in the femoral vein, femoral artery and thoracic duct. Trypsin inhibitor is probably produced by the liver[11,19] and consequently would tend to prevent an increase in trypsin levels in the femoral vein and perhaps in the thoracic duct to a greater extent than in the portal system. Hepatic lymph has been shown to drain into the thoracic duct.[21] The large amounts of pancreatic trypsin liberated into the portal vein, however, probably exceeded the trypsin inhibitor capacity of the portal vein plasma. This might account for the drop in trypsin inhibitor capacity in the portal vein observed in the current investigation.

TABLE 3. *Trypsin Inhibitor Capacity (%) in Plasma and Thoracic Duct Lymph*

Duration of Pancreatitis	Femoral Vein	Thoracic Lymph	Portal Vein
Control	56 ±5.2	57 ±7.9	72 ±4.0
One Hour	61 ±3.9	47 ±6.9	69 ±5.8
Two Hours	64 ±4.8	55 ±7.2	67 ±5.7
Three Hours	64 ±4.8	54 ±7.2	61 ±7.1
Five Hours	63 ±4.1	56 ±9.5	54 ±8.2

In contrast to the changes which were observed in the levels of amylase, lipase, trypsin and trypsinogen, both free and total elastase levels tended to decrease after the induction of pancreatitis. This is consistent with the previous observations of Rinderknecht[15] and Satake *et al.*[17] that plasma elastase activity decreases in patients with acute pancreatitis. Fabiani[6] reported that there was an early significant rise in elastase inhibitor capacity during acute pancreatitis. Consequently it is not clear whether plasma elastase activity decreases following acute pancreatitis because less elastase is liberated from the injured pancreas or whether it is due to an increase in the circulating elastase inhibitor. One would suspect all pancreatic enzymes to be liberated following pancreatic injury so that the failure of release of one enzyme would not be anticipated. The tendency of both free and total elastase levels to decrease in the portal vein while all the other enzymes including trypsin and trypsinogen are increasing might suggest, however, that the pancreas actually liberates less elastase into the circulation following the induction of pancreatitis. It is also possible that elastase is more susceptible to inactivation by other

TABLE 4. *Total and Free Elastase Levels in Plasma and Lymph (microgms/ml ± S. E. mean)*

Duration of Pancreatitis	Femoral Vein (Total)	Femoral Vein (Free)	Thoracic Lymph (Total)	Thoracic Lymph (Free)	Portal Vein (Total)	Portal Vein (Free)
Control	7.9	1.2	3.7	1.6	9.6	2.0
	±1.8	±0.9	±0.5	±0.6	±1.7	±0.7
One Hour	6.0	3.2	4.0	1.5	6.7	3.1
	±0.8	±0.4	±1.4	±0.6	±1.3	±0.8
Two Hours	4.7	2.8	3.4	1.9	4.7	2.5
	±0.8	±0.5	±0.9	±0.5	±0.6	±0.3
Three Hours	3.4	1.9	2.6	1.3	4.2	1.7
	±0.6	±0.4	±1.1	±0.8	±1.0	±0.3
Five Hours	2.1	0.7	1.6	0.8	2.9	1.5
	±0.6	±0.2	±0.8	±0.2	±1.1	±0.9

proteolytic enzymes which are liberated simultaneously. The problem of decreased elastase activity in the portal vein is further complicated by the fact that elastase inhibitor in the portal vein appears to increase following the induction of pancreatitis. The increase which we observed in elastase inhibitor in the portal vein, suggests that trypsin inhibitor is produced in the liver while elastase inhibitor may be produced by some other organ.

The observations of Geokas[7] suggests that the pancreas may be a source of the elastase inhibitor. Our observations on tissue elastase before and after the induction of pancreatitis are consistent with the observations of previous investigators.[7,16] Geokas[7] reported that after three hours of experimental pancreatitis in dogs, 50 mg of pancreatic tissue caused a 13% inhibition of 15 units of crystalline porcine elastase under *in vitro* conditions. The current experiment suggests that the decreased elastase activity in plasma was caused by an increasing elastase inhibitor capacity, originating probably in the pancreas or in another organ within the portal circulation. In this and previous experiments,[16] pancreatic juice was found to have an elastase inhibitor capacity of approximately 50%. These findings suggest that elastase inhibition in the pancreas would protect the gland from the action of free elastase.

These experiments, consequently, suggest that the site of release of elastase and elastase inhibitor may differ from that of trypsin inhibitor. It is suggested that during pancreatitis the pancreas or some other extrahepatic abdominal organ may liberate more elastase inhibitor while the pancreatic output of unbound elastase is reduced. Trypsin inhibitor, on the other hand, appears to be produced by the liver. The decreased level of elastolytic activity in the pancreas following pancreatitis may reflect the dilutional effect resulting from edema fluid formation within the pancreas. The findings, however, are also consistent with a local activation or release of elastase inhibitor within the pancreas.

TABLE 5. *Elastase Inhibitor Capacity (%) in Plasma and Lymph*

Duration of Pancreatitis	Femoral Vein	Thoracic Lymph	Portal Vein
Control	72	76	47
	±3.7	±2.6	±8.2
One Hour	61	78	64
	±6.2	±4.4	±5.7
Two Hours	60	82	76
	±6.4	±0.9	±3.6
Three Hours	61	75	58
	±4.0	±7.8	±7.8
Five Hours	59	62	70
	±5.2	±8.6	±7.6

Summary

The levels of several pancreatic enzymes were measured serially in the plasma and lymph of dogs during a period of 5 hours following bile induced pancreatitis. Plasma amylase, lipase, trypsinogen and trypsin levels rose during the 5 hour period after pancreatitis. Meanwhile plasma total elastase levels decreased to less than half of control values. Free elastase levels in the femoral and portal veins rose slightly in the first hour after which they returned to normal. It was postulated that the decrease in elastase may be partially explained by a decreased liberation of unbound elastase by the pancreas. Since the portal vein levels of elastase inhibitor increased, it was also postulated that an increased output of elastase inhibitor may also partially account for the drop in circulating elastase observed following the induction of pancreatitis. In contrast to elastase inhibitor, trypsin

TABLE 6. *Tissue Elastase (microgms/gm wet weight) (mean ± S.E.)*

Normal Pancreatic Tissue	
Head	150.9 ± 20.5
Body	176.0 ± 22.6
Tail	192.1 ± 14.5
Pancreas	Five Hours After Pancreatitis
Head	104.4 ± 21.1
Body	87.7 ± 16.8
Tail	89.3 ± 26.1

TABLE 7. *The Elastase Inhibitor Capacity (%) in Normal Canine Pancreatic Juice*

Animal Number	1	2	3	4	5	6	7	8	9	10	11	Mean and S. E.
Elastase Inhibitor %	40	52	38	59	54	45	40	59	62	52	50	50 ± 2.2

inhibitor decreased in the portal vein while the trypsin inhibitor in the systemic circulation appeared to increase slightly. As a result of these differences in response in circulating trypsin inhibitor and elastase inhibitor it is suggested that their sites of production may be different.

References

1. Cherry, I. S. and Crandall, L. A., Jr.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury. Amer. J. Physiol., **100**:266, 1932.
2. Christensen, L. K.: A Method for the Determination of Trypsin Inhibitors in Urine and Serum. Scandinav. J. Clin. and Lab. Invest., **10**:177, 1958.
3. Dimbiloglu, M. E., Appert, H. E., Howard, J. M. and Pairent, F. W.: The Relative Tolerance of the Dog to Intravenous Infusions of Pancreatic Juice. Surg., **64**:805, 1968.
4. Egdahl, R. H.: Mechanism of Blood Enzyme Changes Following the Production of Experimental Pancreatitis. Ann. Surg., **148**:389, 1958.
5. Erlanger, B. F., Kokowsky, N. and Cogen, N.: The Preparation and Properties of Two New Chromogenic Substrates of Trypsin. Arch. Biochem. and Biophysic., **95**:271, 1961.
6. Fabiani, P. C., Frossard, S., Lenmit, P., Huguin, M. and Leger, L.: Diagnostic Value of Estimation of Lipase and Elastase Inhibitor in Pancreatic Disease. Press. Med., **77**: 1507, 1969.
7. Geokas, M. C., Murphy, D. R. and McKenna, R. D.: The Role of Elastase in Acute Pancreatitis. I. Intrapancreatic Elastolytic Activity in Bile Induced Pancreatitis in Dogs. Arch. Path., **86**:117, 1968.
8. Geokas, M. C.: The Role of Elastase in Acute Pancreatitis. II. Intrapancreatic Elastolytic Activity in Trypsin Induced Pancreatitis in Dog. Arch. Path., **86**:127, 1968.
9. Geokas, M. C.: The Role of Elastase in Acute Pancreatitis. III. The Destructive Capacity of Elastase on Pancreatic Tissue In Vivo and In Vitro. Arch. Path., **86**:135, 1968.
10. Howard, J. M., Smith, K. A. and Peters, J. J.: Acute Pancreatitis: Pathways of Enzymes into the Blood Stream. Surgery, **26**:161, 1949.
11. Laurell, C. B. and Erikson, S.: The Electrophorectic Alpha-I-Globulin Pattern of Serum in Alpha-I-Antitrypsin Deficiency. Scandinav. J. Clin. and Lab. Invest., **15**:132, 1963.
12. Morgan, A., Robinson, L. A. and White, T. T.: Postoperative Changes in the Trypsin Inhibitor Activities of Human Pancreatic Juice and the Influence Infusion of Trasylol on the Inhibitor Activity. Amer. J. Surg., **115**:131, 1968.
13. Nardi, G. L. and Lees, C. W.: Serum Trypsin: A New Diagnostic Test for Pancreatic Disease. New Engl. J. Med., **258**:799, 1958.
14. Resnick, M., Lapp, N. L. and Morgan, W. K. C.: Serum Trypsin Inhibitor Concentrations in Coal Miners with Respiratory Symptoms. JAMA **215**:1101, 1971.
15. Rinderknecht, H., Geokas, M. C., Silverman, P. and Haverback, B. J.: Determination of Elastolytic Activity in Blood and Normal Subjects and Patients with Acute Pancreatitis. Clin. Chim. Acta., **19**:89, 1968.
16. Satake, K., Carballo, J., Appert, H. E. and Howard, J. M.: Elastase Activity in Pancreatic Juice and Plasma of the Dog. Arch. Surg., **104**:64, 1972.
17. Satake, K., Carballo, J., Appert, H. E. and Howard, J. M.: Plasma Elastoylytic Enzyme Activity in Pancreatic Disease. Arch. Surg., **104**:62, 1972.
18. Sharp, H. L., Bridges, R. A. and Krivit, W.: Cirrhosis Associated with Alpha-I-Antitrypsin Deficiency: A previously Unrecognized Inherited Disorder. J. Lab. Clin. Med., **73**:934, 1969.
19. Somogyi, M.: Blood Diastase as an Indicator of Liver Function. Proc. Soc. Exper. Biol. and Med., **32**:538, 1934.
20. Surianu, P., Tragor, S. and Lenghel, A.: Behavior of Elastase of Anti-Elastase and of the Fifth Enzymatic Fraction in Patients with Chronic Pancreatitis. St. Cerc. Med. Int., **10**:439, 1969.
21. Vega, R. E., Appert, H. E. and Howard, J. M.: Effect of Secretin in Stimulating the Output of Amylase and Lipase in the Thoracic Duct of the Dog. Ann. Surgery, **166**:995, 1967.

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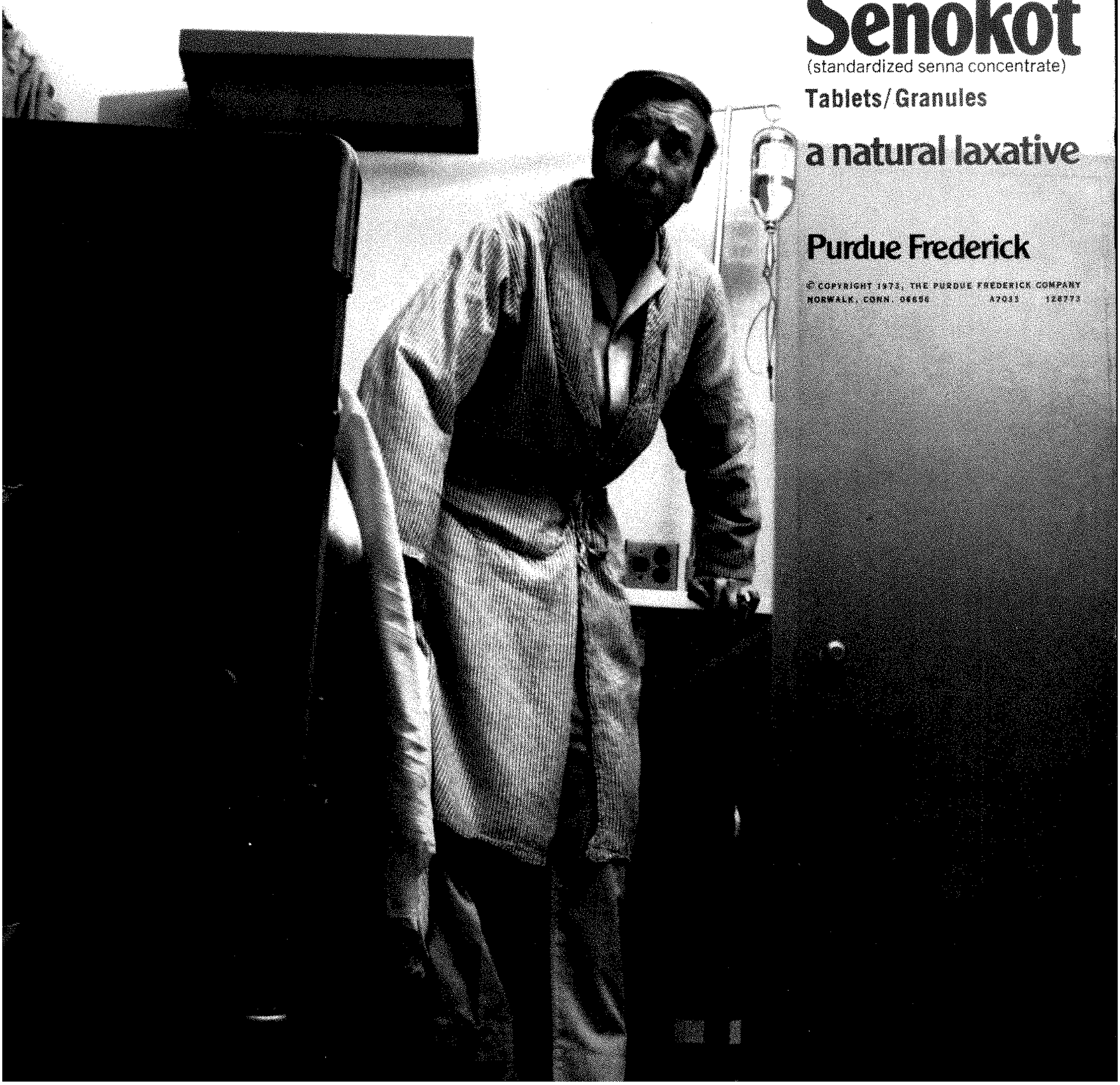

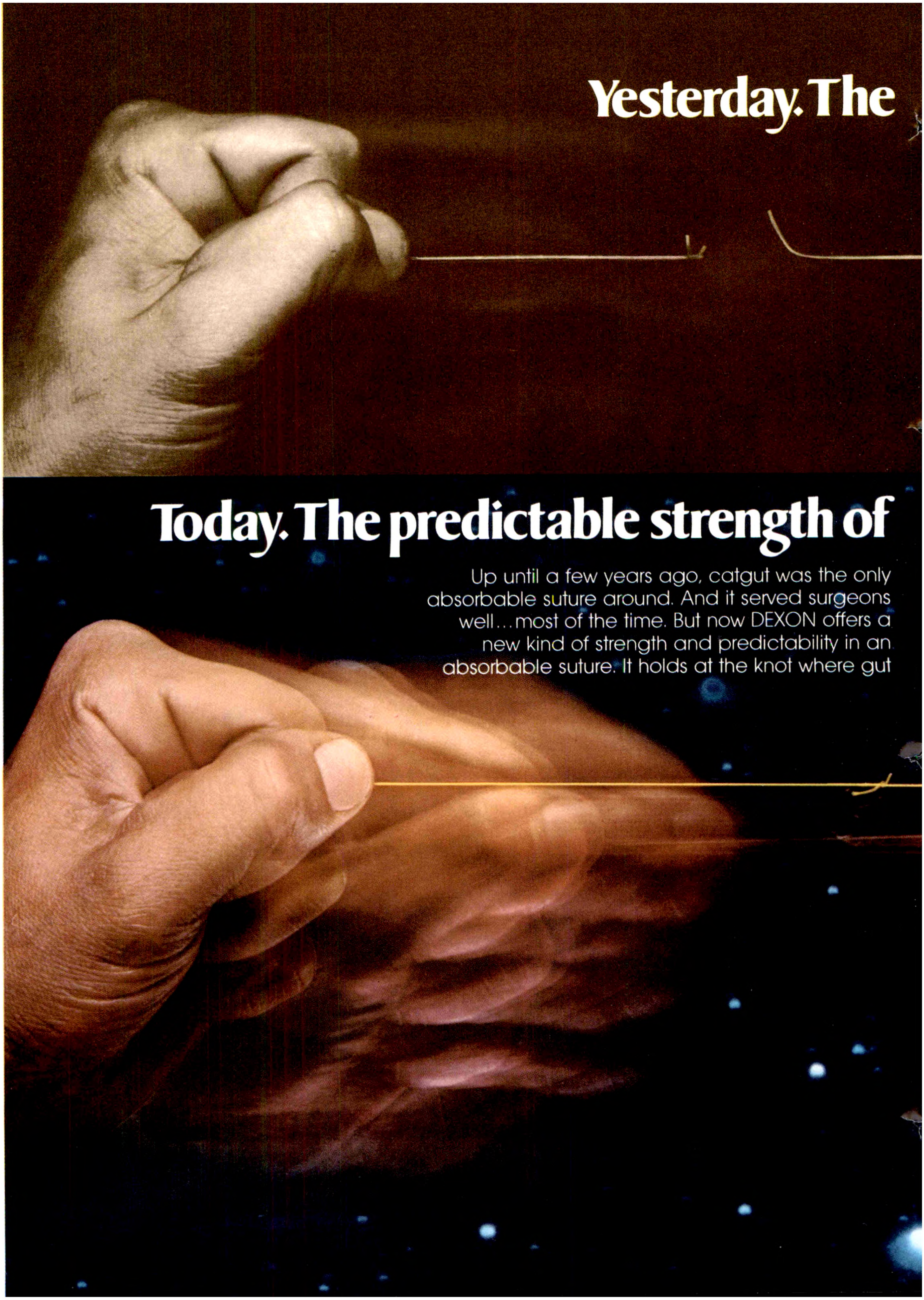
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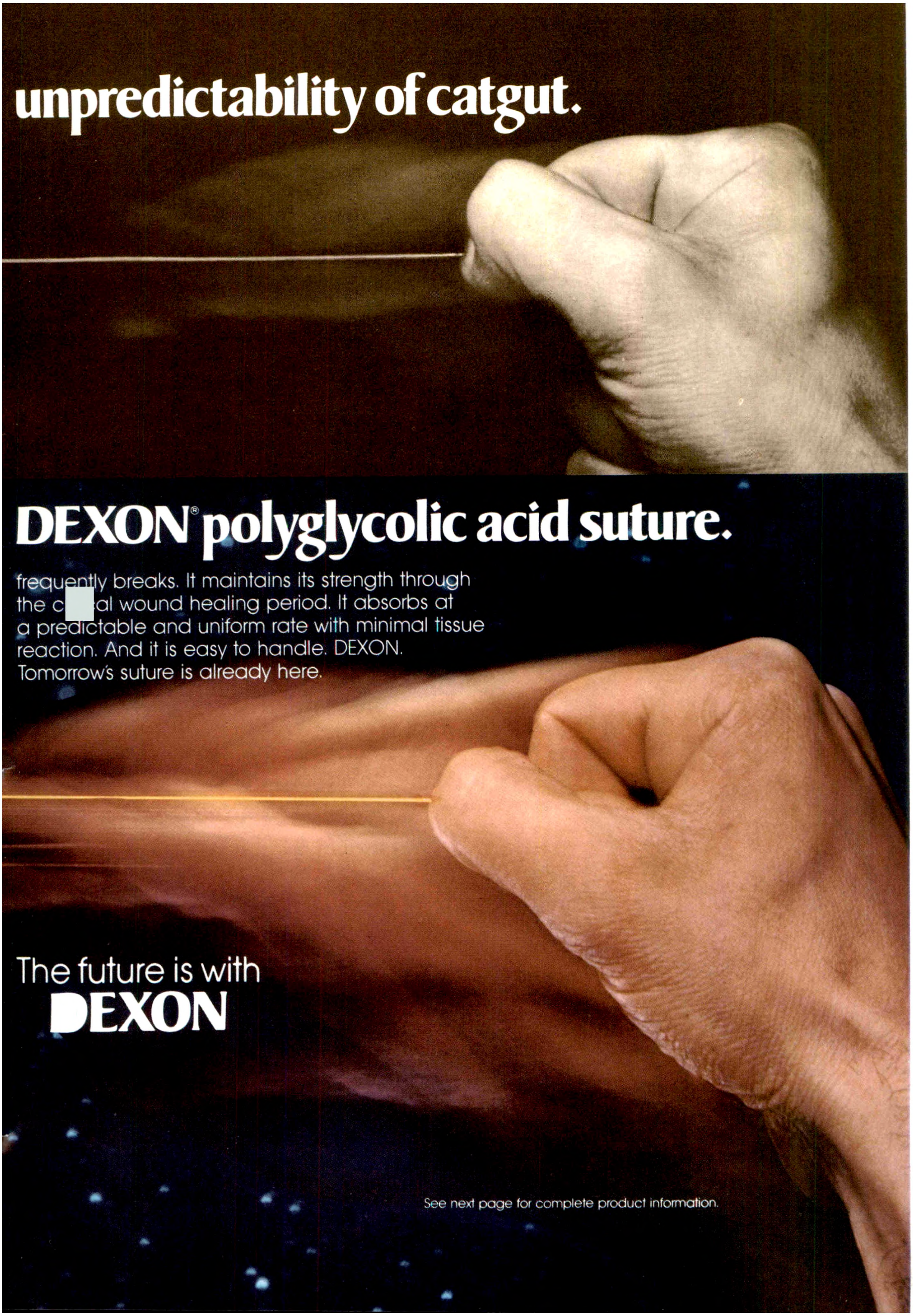

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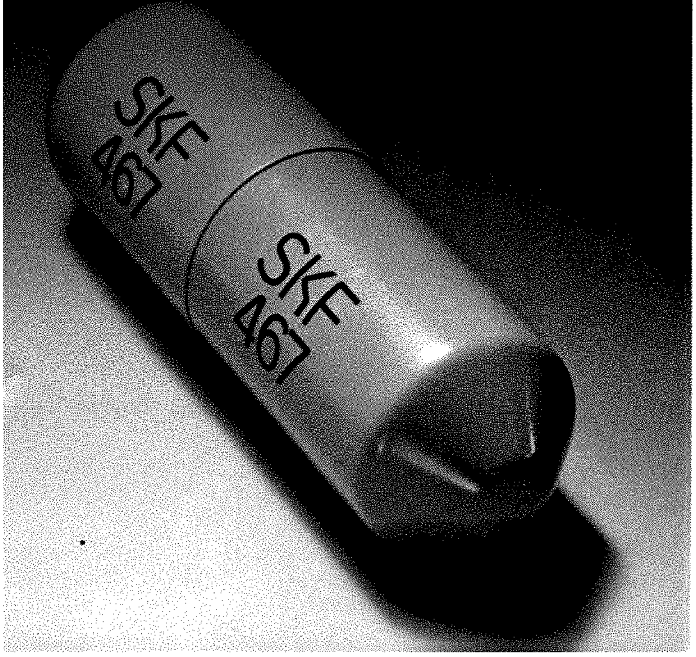

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due to susceptible strains of *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, and some strains of *Enterobacter* and enterococci

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due to susceptible strains of *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci

See prescribing information for additional indications and susceptible organisms.

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peak serum levels of 37.9 and 63.8 mcg./ml. respectively were obtained one to two hours following 500-mg. and 1-Gm. I.M. doses of cefazolin

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Kefzol is contraindicated in patients with known allergy
to cephalosporins and should be given with great caution to
penicillin-allergic patients.

Please see following page for summary of prescribing information.

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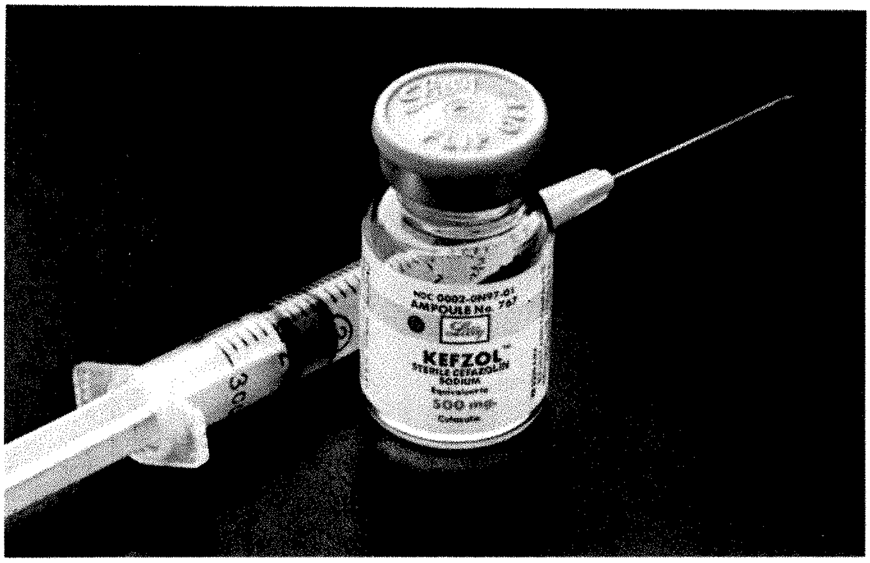

Description: Kefzol™ (cefazolin sodium, Lilly) is a semisynthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-8-oxo7-[2-(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

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Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole-positive *Proteus* (*Pr. vulgaris, Pr. morganii, Pr. rettgeri*) are resistant. Methicillin-resistant staphylococci, *Serratia, Pseudomonas, Mima,* and *Herellea* species are almost uniformly resistant to cefazolin.

Indications: Kefzol is indicated in the treatment of the following serious infections due to susceptible organisms:

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Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Kefzol is effective in the eradiction of streptococci from the nasopharynx; and some strains of *Enterobacter* and enterococci

Skin and soft-tissue infections due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci

Bone and joint infections due to *Staph. aureus*

Septicemia due to *D. pneumoniae, Staph. aureus* (penicillin-sensitive and penicillin-resistant), *Pr. mirabilis, Esch. coli,* and *Klebsiella* species

Endocarditis due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Kefzol™ (cefazolin sodium, Lilly).

Contraindication: KEFZOL IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

Warnings: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Kefzol, cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

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have been reported:
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vulvar pruritus, and eosin
occurred.
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levels has been observed
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Other—Pain at the site
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some with induration. Phl
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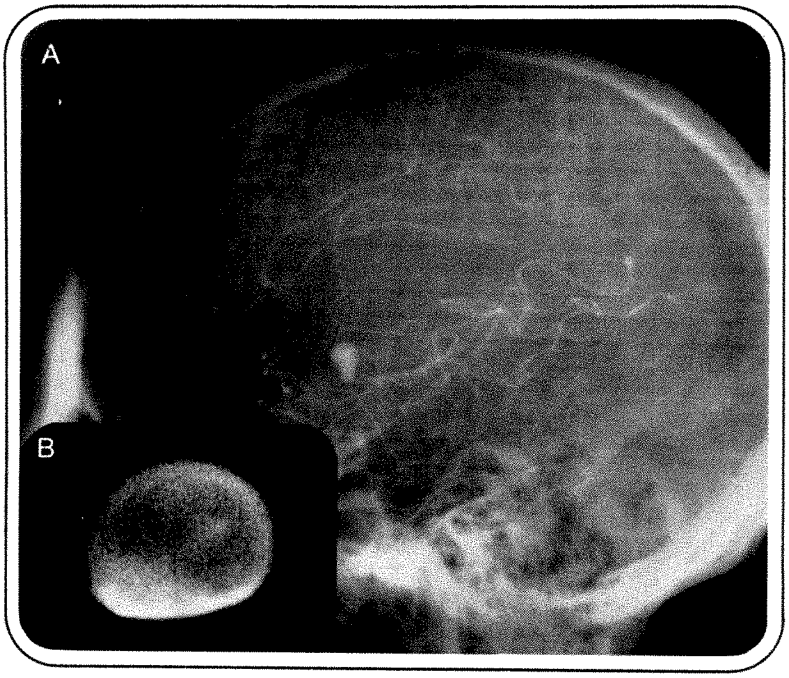

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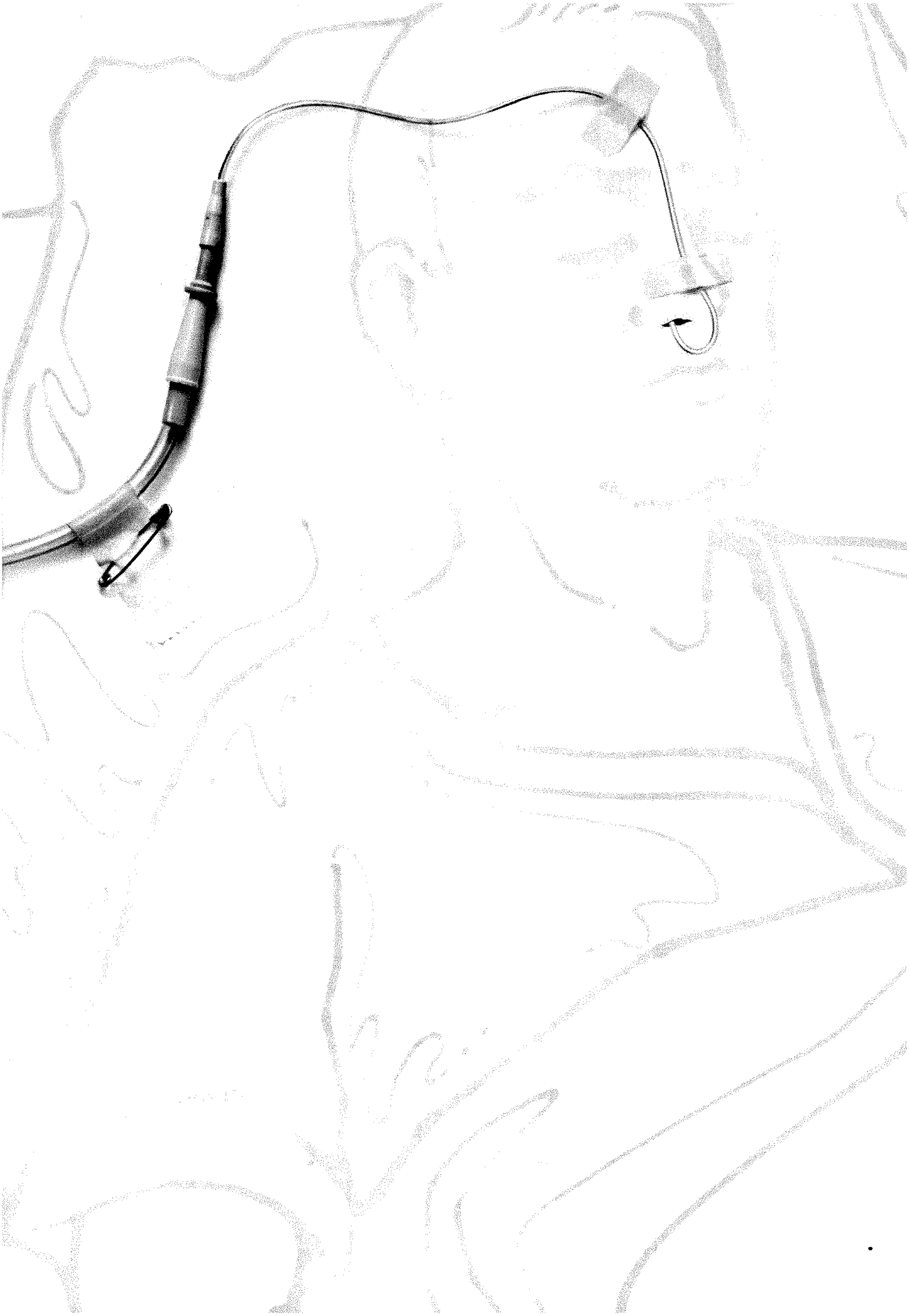

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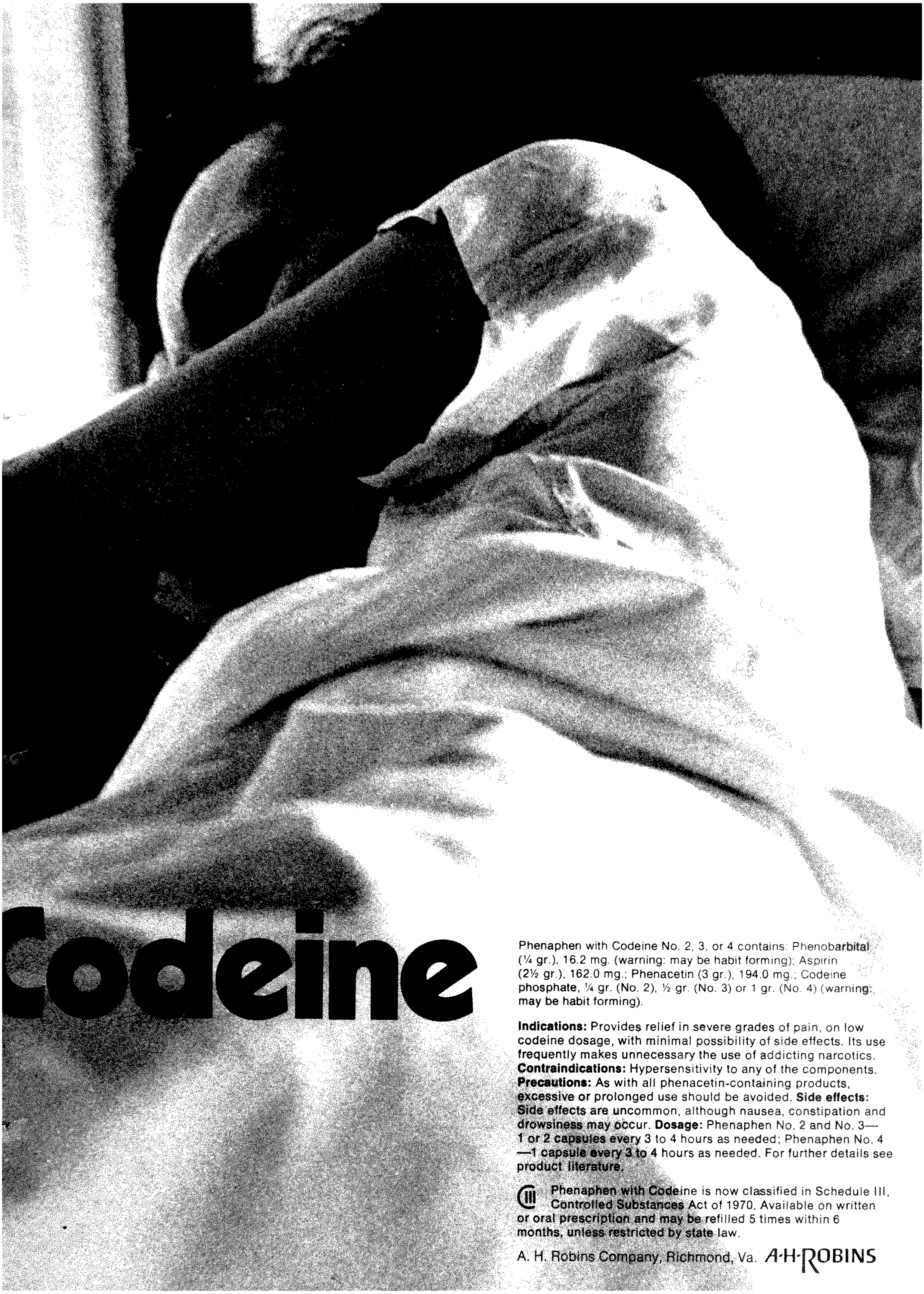

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Coronary Artery By-pass Surgery and Renal Transplantation:

A Case Report

JAMES O. MENZOIAN, M.D., ROBERT C. DAVIS, M.D.,
BELDON A. IDELSON, M.D., JOHN A. MANNICK, M.D.,
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RENAL TRANSPLANTATION is generally reserved for those patients who have terminal renal failure without other major systemic diseases.[4,6] However, there have been recent reports of successful kidney transplantation in patients suffering from renal failure secondary to diseases which involve other organ systems. These include diabetic glomerulosclerosis,[8] Fabrey's disease,[3] amyloidosis,[1] and lupus erythematosus.[10] We are not aware of prior successful renal transplantation in patients with life-threatening coronary artery disease and therefore report the successful surgical rehabilitation of a patient with angina decubitus and end-stage renal failure.

Case Report

C.D., a 47-year-old white mother of 4, was first admitted to University Hospital in March, 1971 because of arteriosclerotic and hypertensive cardiac disease and chronic renal failure. She gave a history of enuresis to age 14, multiple episodes of acute pyelonephritis starting at age 16, and preeclampsia with each of her 4 pregnancies. At age 41, she had been hospitalized elsewhere for an acute myocardial infarction. An IVP obtained at that time revealed a normal right kidney and an atrophic left kidney. Over the next 6 years she developed progressive renal failure and increasing angina despite treatment with nitroglycerin and long acting nitrates. The family history revealed that the patient's mother died at age 54 from coronary artery disease. The patient had 2 brothers with coronary artery disease, 1 brother with diabetes mellitus, 1 sister who had hypertension and a second sister who had had a stroke.

At the time of her first University Hospital admission she had a blood urea nitrogen of 55 mg %, and a serum creatinine of 8.5 mg %. Her urine had a specific gravity of 1.009, a pH of 6.0, no sugar, 3+ protein and an active urinary sediment with white blood cells, renal tubular cells and granular and hyaline casts. An infusion IVP revealed two small kidneys with irregular contours; the right kidney measured 10.2 cm and the left kidney measured 7.2 cm. Her hematocrit was 32%. She had a Frederickson Type II lipid profile. Her electrocardiogram indicated a normal sinus rhythm and left ventricular hypertrophy with evidence of a prior anteroseptal myocardial infarction. Her blood pressure was 170/110. Her diagnosis at this time was arteriosclerotic heart disease, progressive disabling angina and moderate renal insufficiency secondary to chronic pyelonephritis.

Over the next few months, the patient's angina rapidly progressed to angina decubitus and required up to 100 nitroglycerin tablets per week and her serum creatinine rose to 9.9 mg %. It was felt that the patient's angina was clearly severe enough to warrant coronary angiography for evaluation of possible coronary artery reconstruction but her marginal renal function made such an undertaking questionable. At the same time it was felt that the patient could be considered a candidate for renal transplantation only if her coronary artery insufficiency were corrected. The decision was made to evaluate her for coronary artery revascularization with the understanding that if this surgery were successful she would be accepted for renal transplantation.

Coronary angiography indicated normal left and right heart pressures, total occlusion of the left anterior descending coronary artery with retrograde filling through collaterals from the circumflex artery and a vestigal right coronary.

She was prepared for coronary artery revascularization by peri-

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toneal dialysis. An aorto-left anterior descending coronary artery saphenous vein by-pass graft was done with cardiopulmonary by-pass. The blood flow in the vein graft, determined by a electromagnetic flow meter, was 60–70 ml per minute.

Late in the afternoon of the day of surgery the patient again underwent peritoneal dialysis. By the fourth postoperative day the patient had reached her preoperative level of renal function. The remainder of her postoperative course was uneventful and she was discharged, free of angina, on the fifteenth postoperative day on a 4 gram protein diet.

Over the next 5½ months she was maintained on intermittent peritoneal dialysis. Repeat coronary angiography revealed patency of the graft with good distal run-off. Six months after her coronary artery surgery she had a radial artery to cephalic vein shunt placed in her right arm, and began hemodialysis. Eight months following coronary surgery the patient again developed mild angina associated with ST-depression on the electrocardiogram. Her hematocrit at this time was 16%. The angina disappeared after red cell transfusion but would recur when her hematocrit fell below 20%.

She was found to have an HL-A identical brother who readily consented to donate his kidney. On May 30, 1972 she underwent posterior bilateral nephrectomy in preparation for renal transplantation. Microscopic evaluation of her kidneys indicated chronic pyelonephritis. Her postoperative course was uneventful and she was discharged on the 12th postoperative day. Renal transplantation was performed in July, 1972, 15 months after her aorto-coronary by-pass graft. Renal arteriography showed that both kidneys of the donor had two renal arteries from the aorta. The end of the smaller artery to the donor's left kidney was anastomosed to the side of the major left renal artery, using the Kunlin technique, and the major renal artery was anastomosed, end to side, to the external iliac artery of the recipient. The renal vein was anastomosed to the side of the external iliac vein and a ureteroneycytostomy was performed. There was immediate urine output and early function. No further hemodialysis was needed. She initially received 3 mg/kg of azathioprine and 60 mg of prednisone per day. Both of these drugs were gradually reduced. At 5 months after transplantation she was receiving 150 mg of azathioprine and 10 mg of prednisone. At that time her creatinine was 1.2 mg %, her BUN 25 mg %, her hematocrit 39% and her blood pressure in the normal range. Twenty-four hour urine collection revealed no protein. She was symptom free.

Discussion

The patient reported above had serious disease of 2 vital organ systems, both potentially correctable. Although both her cardiac disease and her renal disease were rapidly progressing, the cardiac disease posed the most immediate threat to her life. Moreover, we felt that this patient could not be rehabilitated by dialysis or renal transplantation, unless her coronary artery disease were corrected. However, the risk of coronary artery by-pass in a patient with end-stage renal disease was not well established. There are reports of pericardectomy for uremic constrictive pericarditis[2,9] in patients being treated by peritoneal or hemodialysis for end-stage renal disease. Some of these patients have undergone subsequent renal transplantation.[11] Manhas *et al.*[5] also reported 2 patients who had open heart surgery and aortic valve replacement while on chronic hemodialysis. We have recently learned of a 19-year-old female who underwent aortic valve replacement while c peritoneal dialysis and subsequently received a succes ful renal transplant.[7] We were unable to find a reporte case of aorto-coronary by-pass surgery as a prelu to renal transplantation, despite the fact that corona atherosclerosis is the most common cardiac disease the adult population.

The most signficant problem in our patient's manag ment after successful coronary revascularization w the fact that angina reoccurred when her hematocr fell below 20%. This made maintenance hemodialys difficult since frequent transfusions were required maintain this level of hematocrit. It therefore appeare logical to proceed with the original plan and offer t patient renal transplantation. The HL-A identic kidney transplant from her brother functioned well an at 5 months after renal transplantation and 20 mont after coronary artery by-pass surgery, she was rehabil tated with normal renal function and without angina.

Previously, patients with end-stage renal disease an life threatening heart disease, have not been considere acceptable candidates for renal transplantation. T successful rehabilitation of our patient who had lif threatening, rapidly progressive angina and progressi end-stage renal disease suggests that other patien with these two relatively common disorders could rehabilitated by sequential corrective surgery.

References

1. Cohen, A. S., Bricetti, A. B., Harrington, J. T., *et al.*: Re Transplantation in Two Cases of Amyloidosis. Lancet, 513, 1971.
2. Collins, H. A., Killen, D. A., Gobbel, W. G., *et al.*: Pe cardectomy for Uremic Pericardial Tamponade. A Thorac. Surg., 9:327, 1970.
3. Desnick, R. J., Allen, K. Y., Simmons, R. L., *et al.*: Corre tion of Enzymatic Deficiencies by Renal Transplantatio Fabrey's Disease. Surg., **72**:203, 1972.
4. Hume, D. M., Idem, p. 112.
5. Manhas, D. R. and Merendino, K. A.: The Management Cardiac Surgery in Patients with Chronic Renal Failu J. Thorac. Cardiovasc. Surg. **63**:235, 1972.
6. Merrill, J. P.: Medical Management of the Transplant Patie in Human Transplantation by Rapaport, F. T. and Dauss J. New York, Grune and Stratton, Inc., 67, 1968.
7. Monaco, A. P. (personal communication).
8. Najarian, J. S., *et al.*: Transplantation for Diabetic Glomer sclerosis. Transplantation Proc., **5**:799, 1973.
9. Nicckey, W. A., Chinitz, J. L., Flynn, J. J., *et al.*: Surgi Correction of Uremic Constrictive Pericarditis. Ann. Inte Med., **75**:227, 1971.
10. Simmons, R. C., Kjellstrand, C. M., Buselmeier, T. J., *et* Renal Transplantation in High Risk Patients. Arch. Su **103**:290, 1971.
11. Wolfe, S. A., Bailey, G. F. and Collins, J. J.: Constrict Pericarditis following Uremic Effusion. J. Thorac. Card vasc. Surg., **63**:540, 1972.

Plasma Renin Activity in Patients Undergoing Surgery of the Abdominal Aorta

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THE ROLE OF THE RENIN-ANGIOTENSIN SYSTEM in the day to day maintenance of electrolyte homeostasis via aldosterone secretion is reasonably well established.[9] The precise correlation of this mechanism with blood pressure regulation and the pathogenesis of hypertensive disease remains somewhat unsettled. A recent revival of interest in renin has suggested it might play a role in the cardiovascular regulation and electrolyte balance of the anesthetized patient.[13] Increases in plasma renin activity have been noted in patients undergoing anesthesia[3,4] and surgery[14] and some attempt has been made to assign it a role in the hemodynamic changes which occurred.

Previous clinical observations suggested that a considerable number of patients undergoing aortic surgery experience postoperative hypertension. In addition, cross clamping of the infrarenal aorta has been shown to decrease renal blood flow,[12,15] undoubtedly one of the many factors in the potential development of renal failure in this group of patients. Plasma renin activity was measured in individuals prior to, during, and after general anesthesia and major surgery of the abdominal aorta to examine possible correlations of renin release with the physiologic events of anesthesia and surgery, cross clamping of the aorta, and postoperative course.

Methods

Twenty-one patients who underwent major surgery of the abdominal aorta were studied. All but 2 were male and ages ranged from 32 to 75 years with a mean of 61 ± S.E. of 2. Surgery consisted of inserting an aortic bifurcation graft following the excision of an abdominal aneurysm; in 3 patients the prostheses were inserted for occlusive aortoiliac disease.

Although no precise measurements of sodium balance were made, none of the patients had been subjected to salt restriction. Three who were receiving diuretic therapy received none for the 48 hours preceding the study. All patients received light premedication consisting of either 5–10 mg. of diazapam or morphine and 0.5–0.6 mg. atropine intramuscularly about one hour prior to the sampling period. Induction of general anesthesia was accomplished with a small intravenous dose (75–100 mg.) of thiopental followed by inhalation of nitrous oxide, oxygen, and halothane. (Two patients received ethrane in clinically similar concentrations (1.0–2.0%).) Following tracheal intubation with the aid of succinlycholine, the anesthetic was maintained with 0.5–1.0% halothane and 50% nitrous oxide and oxygen. Intermittent doses of d-tubocurarine were employed for adequate surgical relaxation.

Four samples for determining plasma renin activity (PRA) were obtained from each patient. Sampling was accompanied via a #20 medicut cannula which was inserted percutaneously into the right radial artery with the aid of local anesthesia and which afforded a means for directly measuring arterial pressure during the procedure. Sample I, the baseline value, was taken prior to the induction of anesthesia. The patients at this time were supine and premedicated following an overnight fast. None had received parenteral fluid prior to arrival in

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the operating room. Sample II was drawn shortly after surgical incision under adequate anesthesia, which occurred about 20–30 minutes after the start of anesthetic induction. Following insertion of the graft and release of the aortic clamp, Sample III was obtained. This represented an average interval of about 90 minutes after Sample II. The final specimen (Sample IV) was taken during the immediate postoperative period in the recovery room. Each 10 cc sample was collected in heparinized glass tube and centrifuged immediately. The plasma supernatant was withdrawn and frozen until its plasma renin activity could be measured. PRA was determined by the method of Gould, *et al.*[8] Advantages of this method are that excess hog renin substrate is added to all samples so that angiotensin generation is independent of substrate concentration and duration of incubation with/and without the addition of a known amount of purified human renin. The extra angiotensin generated by this added renin gives an estimate of the angiotensin generating capacity of the plasma per unit of renin added. It also allows PRA results to be expressed in absolute Goldblatt units rather than the more conventional equivalents of angiotensin generated (nanograms % per given time period). The latter method fails to consider the variable amounts of angiotensin generated per unit of renin in different plasma samples, which reflects the amount of renin-substrate present in the samples.

Statistical methods included analysis of variance as well as Student "t" tests. Linear regression analysis was performed with the aid of a Hewlitt Packard #1018 desk top computer.

Results

Baleline values for plasma renin activity in the 21 patients ranged from 0.06 to 11.86 × 10^{-4} Goldblatt units per milliliter with a mean of 2.37 ± S.E. of 0.64 (henceforth all values for renin activity will be expressed in G. U. × 10^{-4}/ml.). This was significantly greater than obtained from a control laboratory population of 20 healthy volunteers ($P < 0.025$) whose values averaged 0.87 ± S.E. of 0.18. During surgical anesthesia PRA rose significantly ($P < 0.01$) to an average value of 3.52 ± S.E. of 0.64 (Sample II in Fig. 1). A further elevation of PRA to 5.15 ± 0.94 (mean ± S.E.) was noted in Sample III following release of the aortic cross clamp. Specimens were obtained 90–120 minutes after Sample II and thus reflect the additional anesthesia time, surgical manipulation involved in clamping the aorta, securing the graft, and finally releasing the clamp. The final postoperative Sample (IV) showed a decline in the mean values to 3.49 ± S.E. of 0.76, which was still elevated above control values but not significantly ($P > 0.10$).

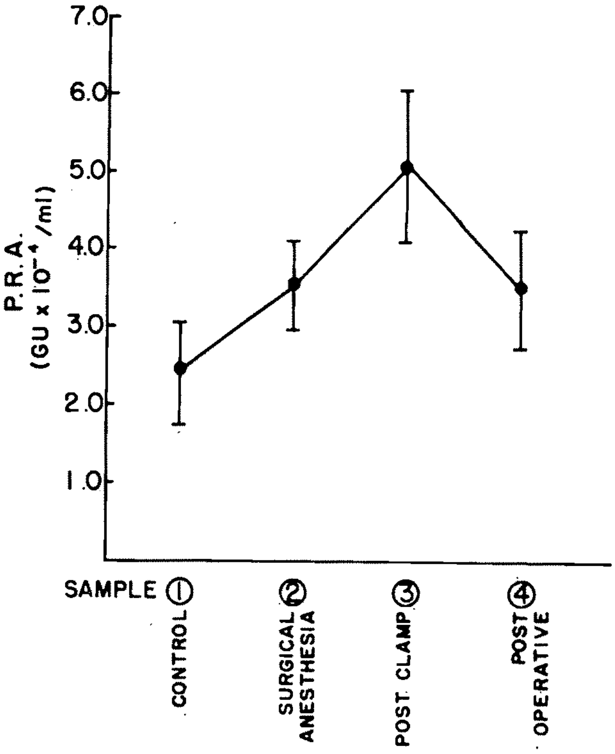

FIG. 1. (Mean ± S.E.)

Blood loss was estimated at 1600 ± 180 milliliters (mean ± S.E.) for all the procedures. The aorta was cross-clamped for an average time of 77 minutes. Following release of the clamped aorta systolic blood pressures fell 15 mm Hg. (±S.E. of 3). No relationship could be established between any of these factors and corresponding changes in PRA.

Six patients underwent bilateral lumbar sympathectomy prior to insertion of the aortic graft. Neither their control values nor their PRA after induction of surgical anesthesia, differed significantly from the remaining population. However, in Sample III, the first obtained after the sympathectomy this group displayed significantly higher ($P < 0.05$) PRA than the patients without sympathectomies (Fig. 2). However, no significant difference was noted in the postoperative Sample (IV). Following release of the aortic clamp the drop in systolic blood pressure was 10 ± 3 mm Hg. (mean ± S.E.) for the sympathectomized patients compared to 17 ± 4 for the remaining patients. Blood loss in both groups did not differ significantly (1600 ml versus 1530 ml; $P > 0.10$).

In the immediate postoperative period significant hypertension (blood pressures in excess of 190/100) was noted in seven patients, an incidence of 33%. (Quite noteworthy was the complete absence of post-operative hypertension in the 6 patients who underwent lumbar sympathectomies.) PRA in these hypertensive patients increased (though not significantly; $P > 0.10$) with surgical anesthesia (Fig. 3) but failed to increase further,

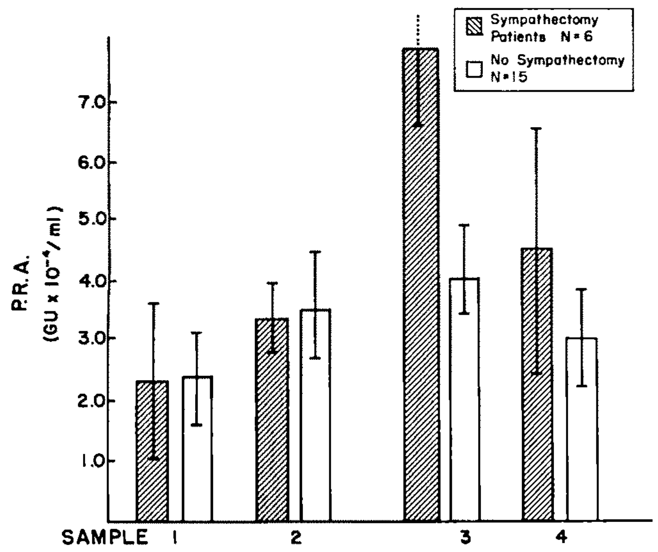

FIG. 2. Effects of sympathectomy on plasma renin activity during aortic surgery. (Mean ± S.E.)

unlike the remaining 14 patients who reached maximal levels in Sample III. None of the changes in PRA in this group of hypertensive patients were significantly different compared to control values. One of these patients, however, developed severe, persistent blood pressure elevations following placement of the aortic graft. A continuous intravenous infusion of trimethaphan was necessary until the following day to control the alarming pressure elevation. PRA in this individual showed a progressive increase, reaching a maximum in Sample IV of eleven times the baseline value.

Most of the patients displayed peak PRA in Sample III; in only 3 patients did it increase in the postoperative Sample (IV). These included the above patient with severe postoperative hypertension and two patients who suffered oliguric renal failure postoperatively. In these latter two PRA reached levels 2.5 to 3 times the control value. When the absolute postoperative values were viewed individually, it was noted that the group of patients with the six highest PRA determinations included 3 patients with postoperative hypertension, one with acute tubular necrosis, and one who had undergone lumbar sympathectomy.

Discussion

Although most of the preoperative measurements of PRA fell between 1.0 and 3.0 × 10^{-4} G.U./ml. there was a rather wide scatter (0.06 to 11.86 × 10^{-4} G.U./ml.). Two patients with the lowest preoperative values, 0.06 and 0.67 respectively were receiving methyldopa therapy because of concern with preoperative blood pressure levels. Significant reductions in PRA have been noted in patients receiving this drug.[10] Stimulation of the sympathetic nervous system is known to promote renin release;[18] it is quite possible the emotional stress of arriving in the operating room for major surgery evoked varying degrees of sympathetic activity in different patients and hence some of the scatter observed in the initial sample. It was hoped that premedication would minimize this effect. The premedicants themselves appear to exert no significant influence on PRA.[5,14]

The significant elevation of PRA noted after induction of surgical anesthesia is not surprising in view of the potential stimuli to renin release. Halothane anesthesia with its accompanying vasodilation may well reduce perfusion pressure in the afferent renal arterioles at the level of the juxta-glomerular apparatus and thus activate the renin-angiotensin system. A significant decrease (38%) in renal blood flow has been measured under halothane anesthesia.[6] To this can be added any reflex symphathetic activity which might occur as a result of surgical stimulation.

Clamping the infrarenal aorta is associated with decreased renal blood flow.[12,15] Whether the changes in renin levels are the cause or the result of the decreased flow is unclear. Nevertheless, releasing the cross-clamped aorta results in a blood pressure drop and the remote possibility of atheromatous emboli.[11] Operative blood loss is also an important consideration at this time[16] although its effect would not be the same as outright hemorrhage since volume replacement was carried out simultaneously. Further influencing intravascular volume and hence renin is the retraction of the viscera necessary for surgical exposure. Thus the peak values seen in most patients during the post clamp period (Sample III) reflect the influence of multiple factors.

Postoperatively PRA declined somewhat, although in all but 5 patients it was still above the baseline value. An expansion of intravascular volume as a result of intraoperative fluid administration offers a possible ex-

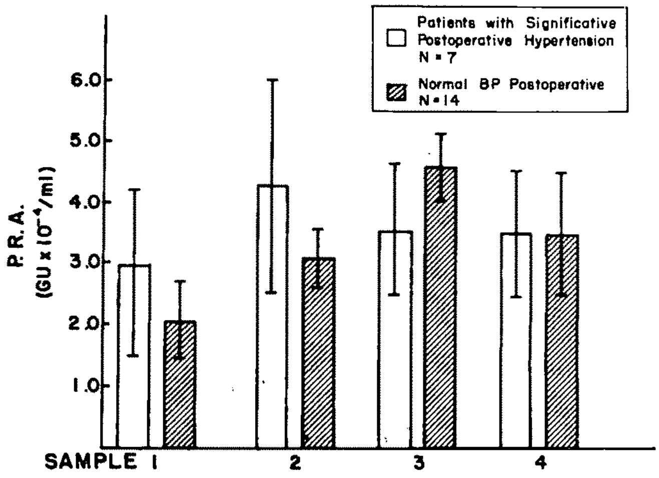

FIG. 3. Plasma renin activity in patients having significant postoperative hypertension. (Mean ± S.E.)

planation for a decrease in renin. There is, however, no significant relationship between the amount of positive fluid balance* and plasma renin activity ($R = 0.04$; $P > 0.10$). Perhaps some of the explanation for the declining values lies in the fact that most of the postoperative samples were obtained shortly after noon. PRA exhabits a normal diurnal decrease in the afternoon.[7] In light of this, the elevated postoperative samples would appear more significant.

Significant postoperative hypertension occurred in 7 (33%) of our patients all of whom had a prior history of hypertension. Hypertension following aortic surgery is not surprising since most of the patients are elderly and have significant cardiovascular disease. Other contributing factors include the large volumes of blood and fluid administered as well as the cross clamping of the aorta and possibility of atheromatous emboli. As a group the hypertensives did not exhibit any dramatic difference with respect to PRA compared to the remaining patients. The hypertension in these patients though significant in degree was self-limited and associated with no morbidity. The only exception to this was the patient mentioned previously whose renin levels rose progressively and who required prolonged therapy with trimethaphan to control blood pressure because of concern for bleeding and the threat of congestive failure. This was interesting in view of the supposedly higher incidence of cardiovascular complications in patients with high renin levels.[9]

The role of the sympathetic nervous system in renin release is well established. Lumbar sympathectomy by removing a portion of this system might be expected to decrease the responsiveness of the renin-angiotensin system. In view of this the significantly greater elevation of PRA following sympathectomy (Fig. 2) are puzzling. A greater operative blood loss or greater drop in blood pressure after releases of the aortic clamp could possibly explain this. Blood loss did not differ in the 2 groups and the blood pressure drop after release of the aortic cross clamp was greater in the patients who did not receive a sympathectomy. The levels of PRA seemed to parallel the severity of vascular disease since sympathectomy was performed in patients with severe arteriosclerosis and occlusive arterial disease. These patients may have a greater likelihood of atheromatous emboli to the renal arteries. Again it must be mentioned that none of these patients experienced postoperative hypertension and their postoperative PRA values showed a relative decline. The opposite might be expected in the face of emboli. Mechanical removal of the sympathetic chain could conceivably produce transient sympathetic stimulation via the renal nerve and consequent renal vasoconstriction and increased PRA. Some interest in this hypothesis is aroused by the findings of a previous study,[14] which demonstrated the highest elevation of PRA during a lumbar sympathectomy.

Susceptibility to acute renal failure is often associated with increased PRA a relationship which has led to the suggestion of a causal role.[2] Unfortunately, the picture is clouded by the fact that the very events which can cause acute renal failure (hemorrhage, surgery, diuresis) are the same stimuli which provoke renin release. Sympathetic stimulation, acute tubular necrosis, and renin secretion all either reflect or effect changes in the distribution of intrarenal blood flow. Acute oliguric renal failure occurred postoperatively in two patients who showed a steady increase in PRA reaching a maximum postoperatively of 2.5 to 3.0 times the control value. The increase may have been more dramatic had the patients not received drugs which lower renin activity.[10,17] One had received alpha methyl dopa preoperatively in large doses while the second received a large bolus of manitol intraoperatively.

The increased levels of plasma renin activity noted in our patients supports the belief that the renin-angiotensin system is activated during anesthesia and surgery can thus be called upon to explain at least some of the changes in fluids and electrolytes and regional hemodynamics which occur. Renin secretion is altered by such factors as blood loss and volume replacement as well as sympathetic stimulation from surgical stress. All of these cloud the picture and make it difficult to assign renin a causative role in such phenomena as hypertension and acute renal failure. Nevertheless it does deserve a place in the present day synthesis of these disorders.

Summary

Plasma Renin Activity (PRA) was measured in 21 patients prior to, during, and after major surgery of the abdominal aorta. The induction of surgical anesthesia was accompanied by a significant rise in PRA. A further elevation occurred (in most patients a peak level was reached) following the insertion of the bifurcation graft and release of the cross clamped aorta. The final measurements, obtained in the immediate post anesthetic period, reflected a decline in PRA although the values were still above baseline figures.

Some of the factors playing a role in these changes include changes in renal blood flow as a result of anesthesia and surgical manipulation, stimulation of sympathetic nervous system, aortic cross clamping, operative blood loss with its accompanying changes in intravascular volume, as well as a normal diurnal variation which occurs with PRA.

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* Positive fluid balance was determined by subtracting the amount of fluid and blood administered intraoperatively from the urine output, 500 cc assumed insensible loss, and intraoperative blood loss.

Possible relationships between changes in PRA and the development of post operative hypertension, the occurrence of renal failure, as well as the performance of lumbar sympathectomy were explored. Elevations of PRA did not correlate well with the presence of postoperative hypertension. Two patients in the series developed oliguric renal failure postoperatively; both failed to show the decline in PRA seen in almost all other patients. Six patients, who underwent lumbar sympathectomy, had significantly higher PRA following release of the aortic clamp than did the 15 remaining pateints. Post operatively, however, there was no significant difference between these groups.

References

1. Block, M. A., Wakim, K. G. and Mann, F. C.: Circulation Through the Kidney During Stimulation of the Renal Nerves. Am. J. Physiol., **169**:659, 1952.
2. Brown, J. J., Gleadle, R. I., Lawson, D. H., Lever, A. F., Linton, A. L., Macadam, R. R., Prentice, E., Robertson, J. I. S. and Tree, M.: Renin and Acute Renal Failure: Studies in Man. Brit. Med. J., **1**:253, 1970.
3. Deutsch, S., Hickler, R. B., Pierce, E. C. and Vandam, L. D.: Changes in Renin Activity of Peripheral Venous Plasma During General Anesthesia. Fed. Proc., **26**(2): 503, 1967.
4. Deutsch, S., Hickler, R. B. and Vandam, L. D.: Cyclopropane Effects on Renal Function in Normal Man. Anesthesiology, **28**:547, 1967.
5. Deutsch, S., Bastron, R. D., Pierce, E. C. and Vandam, L. D.: The Effects of Anaesthesia with Thiopentone, Nitrous Oxide, Narcotics, and Neuromuscular Blocking Drugs on Renal Function in Normal Man. Brit. J. Anaesth., **41**:807, 1967.
6. Deutsch, S., Goldberg, M., Stephen, C. W. and Wen-Hsien, Wu: Effects of Halothane Anesthesia on Renal Function in Normal Man. Anesthesiology, **27**:793, 1966.
7. Gordon, R. D., Wolfe, L. K., Island, D. P. and Liddle, G. W.: A Diurnal Rhythm in Plasma Renin Activity in Man. J. Clin. Invest., **45**:1587, 1966.
8. Gould, A. B., Skeggs, L. T. and Kahn, J. R.: Measurement of Renin and Substrate Concentrations in Human Serum. Lab Invest., **15**:1802, 1966.
9. Laragh, J. H., Baer, L. E., Brunner, H. R., Buhler, F. R., Sealey, J. E. and Vaughan, E. D.: Renin, Angiotensin and Aldosterone System in the Pathogenesis and Management of Hypertensive Vascular Disease. Am. J. Med., **52**:633, 1972.
10. Mohammed, S., Fasola, A. F., Privitera, P. J., Lipicky, R. J., Martz, B. L. and Gaffney, T. E.: Effect of Methyldopa on Plasma Renin Activity in Man. Circ. Res., **25**:543, 1969.
11. Moldveen, G. E., Ronimus, M. and Merriam, J. C., Jr.: Cholesterol Embolization from Pathological Curiosity to Clinical Entity. Circ., **35**:946, 1967.
12. Powers, S. R., Boba, A. and Stein, A.: Mechanism and Prevention of Distal Tubular Necrosis Following Aneursymectomy. Surgery, **42**:156, 1957.
13. Price, H. L. and Pauca, A. L.: Effects of Anesthetics on the Peripheral Circulation. *In* Clinical Anesthesia-A Decade of Clinical Progress. L. Fabian, editor. Philadelphia, F. A. Davis Co., 1969.
14. Robertson, D. and Michelakis, A. M.: Effect of Anesthesia and Surgery on Plasma Renin Activity in Man. J. Clin. Endocrinol. Metab., **34**:831, 1972.
15. Sawawala, P. B., Strong, J. M. and Keats, A. S.: Surgery of the Aorta and its Branches. Anesthesiology, **33**:229, 1970.
16. Skillman, J. J., Lauler, D. P., Hickler, R. B., Lyons, J. H., Olson, J. E., Ball, M. R. and Moore, F. D: Hemorrhage in Normal Man: Effect on Renin, Cortisol, Aldosterone, and Urine Composition. Ann. Surg., **166**:865, 1967.
17. Vander, A. J. and Miller, R.: Control of Renin Secretion in the Anesthetized Dog. Am. J. Physiol., **207**:537, 1964.
18. Vander, A. J.: Control of Renin Release. Physiol. Rev. **47**: 359, 1969.

Adrenal Hemorrhage During Anticoagulant Therapy

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ADRENAL HEMORRHAGE is a rare complication of anticoagulant therapy which usually brings the patient to death before the diagnosis is made and treatment established. Review of the literature reveals that in the great majority of the reported cases, the diagnosis was an unsuspected finding at postmortem examination;[1–4,6,9,11–13,15] we have been able to find in the world literature only 3 cases in which the diagnosis was established *in vivo*. It is interesting that all 3 patients survived with appropriate treatment.[5,7,16]

To increase the clinical awareness in this catastrophic complication, we are reporting the case history of a patient in whom the diagnosis of acute adrenal insufficiency due to hemorrhage during anticoagulant therapy, was established by clinical and laboratory findings, and who survived with medical treatment.

Case Report

A 79-year-old Sicilian female had a right radical mastectomy for carcinoma of the breast. Pathological examination of the specimen revealed no residual tumor at the line of the excisional biopsy; all the lymph nodes were also clear. She did well until the fourth postoperative day when she developed a sudden episode of left chest pain; at physical examination the only positive finding was a slight tenderness in the right calf. The chest X-ray revealed exaggeration of bronchovascular markings of the left base. The following day, the tenderness in the right calf had increased and anticoagulation was instituted with heparin, 75 mg. q.6 hrs. subcutaneously. On the fourth day of anticoagulation, a bleeding time of 38 minutes was obtained and one dose of heparin was withheld. The following morning moderate bloody drainage was observed on the dressing of the mastectomy; the patient complained of back pain; anticoagulation was continued. The following night, now the sixth day of anticoagulation, the patient developed an acute and severe exacerbation of the back pain, mainly at the level of D11 and D12; she was pale, dyspneic and nauseated; her temperature which had been normal had risen to 101°, the heart rate was 110/m. and the blood pressure fell from 160/70 to 116/50mm. Hg. The abdomen was distended and there was some tenderness in the epigastrium, rectal examination revealed normal colored stools. Hemoglobin was 5.5 gm. and hematocrit was 19. The clinical picture closely resembled the one seen in a ruptured aortic aneurysm, but no pulsating masses had been felt in the abdomen on admission and none could be felt now; a radiogram of the abdomen revealed a calcified aorta of normal configuration. No clear diagnosis could be established; because of an old history of dyspepsia a gastrointestinal bleeding was suspected: anticoagulation was suspended and whole blood was transfused. The following morning the hemoglobin had returned to above 10 gm., the abdomen remained soft but distended and again normal colored stools were obtained at rectal examination. The blood pressure, however, remained unstable, the temperature had risen to 103° and the patient was very drowsy and in a few hours became lethargic. With this clinical picture, a massive adrenal hemorrhage was strongly suspected and after drawing blood for laboratory confirmation, treatment was instituted with intravenous normal saline and hydrocortisone, further blood transfusions and antibiotics. The laboratory, during the next 24 hours, submitted the following results: Blood sugar—58 mg.; BUN—36mg; CO_2—22; sodium—126; chloride—88; potassium—3.2 meq; eosinophil count—250/mm^3 (normal up to 50).

After 24 hours of treatment the condition of the patient dramatically improved. In the following days, the cortisone dose was reduced from the initial 400 mg. per/day I.V. and then substituted with Prednisone p.o.; fluorocortisone was also added. The

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patient progressed well and was discharged three weeks after the acute episode, on replacement therapy. Before discharge, 24-hour urinary 17OH were 1.4mg. and 17K were 1 mg.; the skin was noted to have taken on a definite dark discoloration.

Twice in the months following discharge, the patient was readmitted for acute adrenal insufficiency. On both occasions the patient had failed to take the Prednisone tablet, once because she was nauseated and once when she went away on a weekend trip and forgot to take along her medication. Both times she presented with high temperature, drowsiness and low blood pressure; both times she was prompty revived with normal saline and cortisone intravenously. Last year the patient developed an acute myocardial infarction from which she recovered. At present she is 3 years after the radical mastectomy without evidence of recurrence of the breast carcinoma and on continous Prednisone medication.

Discussion

The possibility of an adrenal hemorrhage in this patient was first considered 24 hours after the onset of the severe acute episode of back pain and shock. This suspicion was based on 3 clinical findings: the consideration that blood pressure remained unstable despite adequate blood replacement; the rising temperature in the absence of infection, and the observation that the patient in a short time became drowsy and then lethargic.

In retrospect, the severe back pain which ushered the catastrophe, should have alerted us to this possibility once the diagnosis of ruptured aortic aneurysm had been ruled out; however, this important diagnostic element was unfortunately underestimated and caused a 24-hour delay in considering the proper diagnosis.

Amador[1] in 1965, published a comprehensive review of all the recorded cases of adrenal hemorrhage occuring during anticoagulant therapy. He collected 20 cases from the world literature and added 10 cases from his own institution. In three of the collected cases, the diagnosis was made *in vivo*.[5,7,16] We have been able to collect 19 more cases: in all these patients the diagnosis was made at autopsy.[2–4,6,9,11–13,15] Another case with survival was published by Planques[14] in 1959. In reading this case history one wonders if it could not have been the same case published by Decourt[5] in 1960. In a case reported by Klassen[8] adrenal insufficency of gradual onset occurred after an episode of retroperitoneal hemorrhage associated with anticoagulant therapy.

This complication has been observed both with heparin and coumadin treatment; in many of the published cases, anticoagulation was well beyond theapeutic range before the catastrophic event. Almost invariably, the presenting sign is severe back or flank pain, acute in onset, associated with anorexia, nausea, vomiting and frequently with temperature elevations. Hypotension and impairment of the sensorium follows, the patient may become lethargic, and if corrective treatment is not instituted, almost invariably dies in a short period of time. The laboratory findings reveal a low glucose, low sodium and low chloride and elevated potassium and BUN values. The eosinophil count in those few cases where it was measured was elevated above 50/mm.[3]

The pathogenesis of the hemorrhage in the adrenal parenchyma is not clear, probably it is mainly the consequence of the abnormal coagulation state. The prevalent old age of the published patients, with its attendant increased vascular fragility, and the stress condition arising from the medical or surgical condition for which anticoagulation was required might also play a role since it is known that adrenal hemorrhage may occur spontaneously under stress.[10] Experimentally, it has been shown that ACTH when added to anticoagulants in rabbits increases ten-fold the incidence of hemorrhagic complications.[17]

Judging from the results obtained in the few cases where diagnosis was made, including the present one, the treatment should consist in discontinuation of anticoagulation and generous replacement with steroid, sodium chloride and blood. This medical replacement treatment has been effective in the few cases where it was initiated before coma occurred; however, since usually there is little room for delay, it should be instituted on a clinical suspicion without waiting for laboratory confirmation.

Summary

A patient after radical mastectomy developed deep thrombophlebitis of the leg and was treated with heparin. On the sixth day of anticoagulation she developed a sudden episode of shock, hyperthermia and lethargy. An adrenal hemorrhage was suspected and the patient was treated accordingly with prompt recovery. The laboratory findings confirmed the clinical diagnosis.

References

1. Amador, E.: Adrenal Hemorrhage During Anticoagulant Therapy. Ann. Intern. Med., **63**:559, 1965.
2. Bianchi, C., Camerini, F., Crepaldi, L., *et al.*: Pathologia da anticogulanti. Minerva Cardioangiol., **18**:316, 1970.
3. Castleman, B. and Kibbee, B. U.: Case Records of the Massachusetts General Hospital. New Eng. J. Med., **267**:1140, 1962.
4. Coury, C. H., Thiboult, P. H. and Bourdarias, J. P.: Hematome bilaterâux des capsules surrenales Côeur. Med. Int., **4**:15, 1965.
5. Decourt, J. and Michard, J. P.: Insuffisance surrénale aigüe, puis chronique installée brutalement au cours d'un traitement par l'héparine. Bull Soc. Med. Paris., **76**:422, 1970.

6. Grivâux, M., Diallo, A., Barbier, J., *et al.*: La nécrose hémoragique des surrenales. Sem. Hôp. Paris., **46**:2507, 1970.
7. Harper, J. R., Ginn, W. M. and Taylor, W. J.: Bilateral Adrenal Hemorrhage–Complication of Anticoagulant Therapy, Case Report and Review of the Literature. Amer. J. Med., **32**:984, 1962.
8. Klassen, J. and Murphy, B. E.: Survival After Bilateral Adrenal Hemorrhage During Heparin Therapy. Can. Med. Assoc. J. **97**:1162, 1967.
9. Lansing, P. F.: Adrenal Hemorrhage Associated with Dicumarol Anticoagulation. J. Maine Med. Assoc., **52**:207, 1961.
10. Lawson, D. W., Corry, R. J., Patton, A. S., *et al.*:Massive Retroperitoneal Adrenal Hemorrhage, Surg. Gynecol. Obstet., **129**:989, 1969.
11. Leblanc, M., Michiels, R., Beaufils, J. P., *et al.*: Les Hématomes bilaterâux des glandes surrénales, Complication du traitment anticoagulant. Sem Hôp Paris, **44**:302, 1968.
12. Markle, C. D. and Evans, E. C.: Adrenal Hemorrhage Associated with Anticoagulant Therapy. South. Med. J., **63**: 526, 1970.
13. McDonald, F. D., Myers, A. R. and Pardo, R.: Adrenal Hemorrhage During Anticoagulant Therapy. JAMA, **198**:1052, 1966.
14. Planques, J., Santmarc, R. and Chisin, E.: Insuffisance surrénale apres' héparinotherapie. Annal Méd Légale, **39**: 266, 1959.
15. Reece, R. L.: Bilateral Adrenal Hemorrhage and Calcification of Acute Myocardial Infarction, Report of a Case on Anticoagulant and Steroid Therapy, Hartford Hosp. Bull., **19**: 24, 1964.
16. Thorn, G. W., Goldfien, A. and Nelson, D. H.: The Treatment of Adrenal Dysfunction. Med. Clin. N. Amer., **40**:1261, 1956.
17. Van Couwenberge, G. H. and Jaques, L. B.: Hemorrhagic Effect of ACTH with Anticoagulants. Can. Med. Ass. J., **79**:536, 1958.

Pancreatic Pseudocyst of the Spleen

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ALTHOUGH THE SPLEEN occasionally becomes involved in a pseudocyst of the pancreas by way of forming part of its wall, only 7 published reports have been found of instances in which an intrasplenic cystic lesion has been attributable to pancreatic pathology. These all have been pseudocysts associated with inflammation of the pancreas proper except for 1 case involving heterotopic pancreas which also was probably the site of pancreatitis. Despite its apparent rarity, this lesion is of importance in the differential diagnosis of space-occupying lesions of the spleen. Cognizance of the potential of pancreatitis to produce it, and appropriate diagnostic studies may lead to the more frequent identification of this etiology of splenic lesions. A case is presented in which such a lesion might otherwise have been attributed to embolic infarction secondary to aortic valvular disease.

Case Report

A 47-year-old man was admitted to the Veterans Administration Hospital in Indianapolis on September 17, 1969, 9 days after he had been hospitalized elsewhere for upper abdominal pain, nausea and vomiting. The findings of fever, splenomegaly and the murmur of aortic insufficiency had led to the diagnosis of subacute bacterial endocarditis, institution of treatment with penicillin and streptomycin, and referral of the patient to this hospital. Upon admission, the patient had no acute complaints. He stated that he had felt well until 1 year before this illness when he had experienced the first of three prior episodes similar to the present illness. These were characterized by a few days duration of nausea, vomiting and pain in the left upper quadrant of the abdomen. At no time did he have pleuritic pain or specific symptoms referable to the heart or lungs. During the year, he had noticed increased fatigability and loss of appetite. He had lost 11.4 kg (25 pounds) in weight.

Pertinent past medical history included hospitalization about 10 years previously for fever of undetermined etiology, known hypertension for 5–6 years, and loss of sight in his right eye 9 years before due to central retinal artery occlusion. Alcoholic consumption was stated to be 6 or 7 beers per week for 15 years.

At the time of admission he was afebrile and in no acute distress. The branchial artery blood pressure was 180/110; the heart rate 80 with occasional premature ventricular contractions. Examination of the heart revealed the PMI in the sixth intercostal space 2 cm lateral to the midclavicular line with a heave. A thrill was palpated at the apex; a thrill and shock in the aortic area. A^2 was increased. A IV/VI systolic ejection murmur in the aortic area radiated to the apex; a II/VI diastolic blowing murmur was heard in the second and third right intercostal space. S^4G was present. Fundoscopy disclosed an atrophic optic nerve on the right and grade II hypertensive changes on the left. The spleen was palpably enlarged. Otherwise the physical examination was nonrevealing.

An extensive investigation was pursued into the nature of his hypertension, valvular disease and splenomegaly. No specific etiology of the hypertension was discovered and ultimately it was concluded that he had essential hypertension, hypertensive cardiovascular disease with left ventricular hypertrophy and aortic insufficiency secondary to aortic dilatation. The hypertension responded to treatment with Aldomet^R.[*]

An X-ray of the chest before admission had shown a left pleural effusion. This had cleared by the time of admission. An upper GI series, barium enema and excretory urogram demonstrated no intrinsic abnormality, but did show caudal displacement of the splenic flexure of the colon and of the left kidney by a soft tissue mass. A liver and spleen scintiscan was done using technetium 99m sulfide colloid. No defects were noted in the liver. A large scalloped defect was seen in the upper pole of the spleen on the

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anterior view which, on the left lateral view, presented itself as 2 defects separated by a tongue-like area with decreased activity (Fig. 1). This was considered compatible with a cystic lesion of the spleen, either an abscess or hemorrhagic infarct. A second scan done 22 days later revealed the lesion to have become slightly smaller.

The patient's temperature remained normal on continued antibiotic therapy. Four aerobic and anaerobic blood cultures were sterile. His white blood cell count did not exceed 9,000/cmm with a normal differential. Search for a specific etiology of the splenic lesion including serum protein electrophoresis, bone marrow biopsy, serologic test for syphilis and L E cell preparations

FIG. 1. Scintiscan of the liver and the spleen with Technetium labelled sulfur colloid shows: (A) on the anterior view a large defect of the upper pole of the spleen; (B) on the left lateral view two large defects separated by a tongue like area of activity.

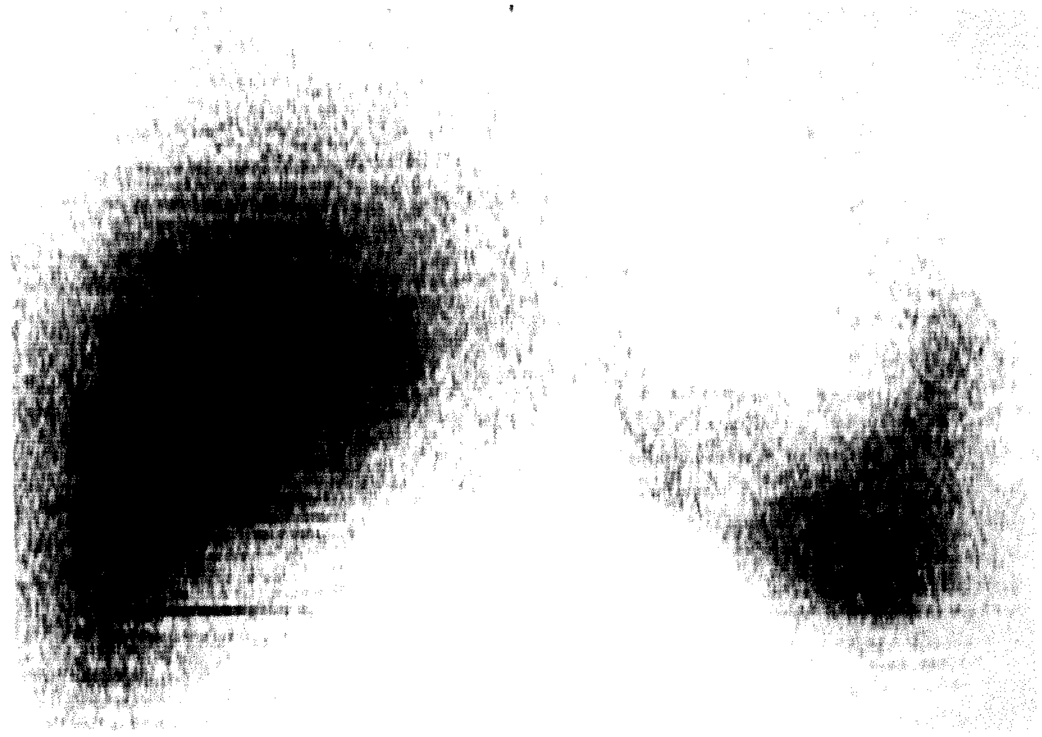

FIG. 1A

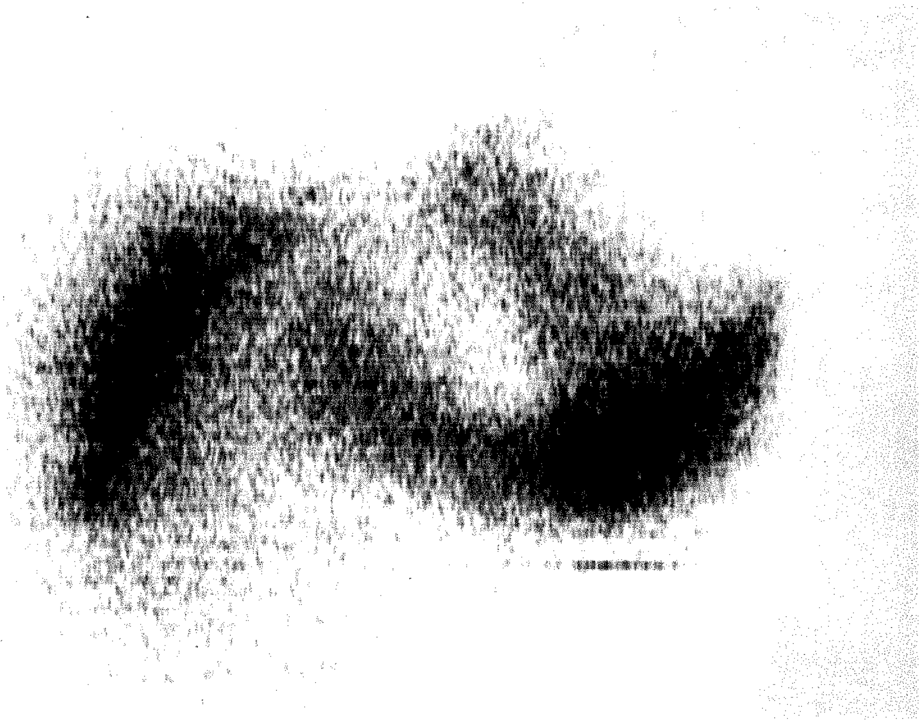

FIG. 1B

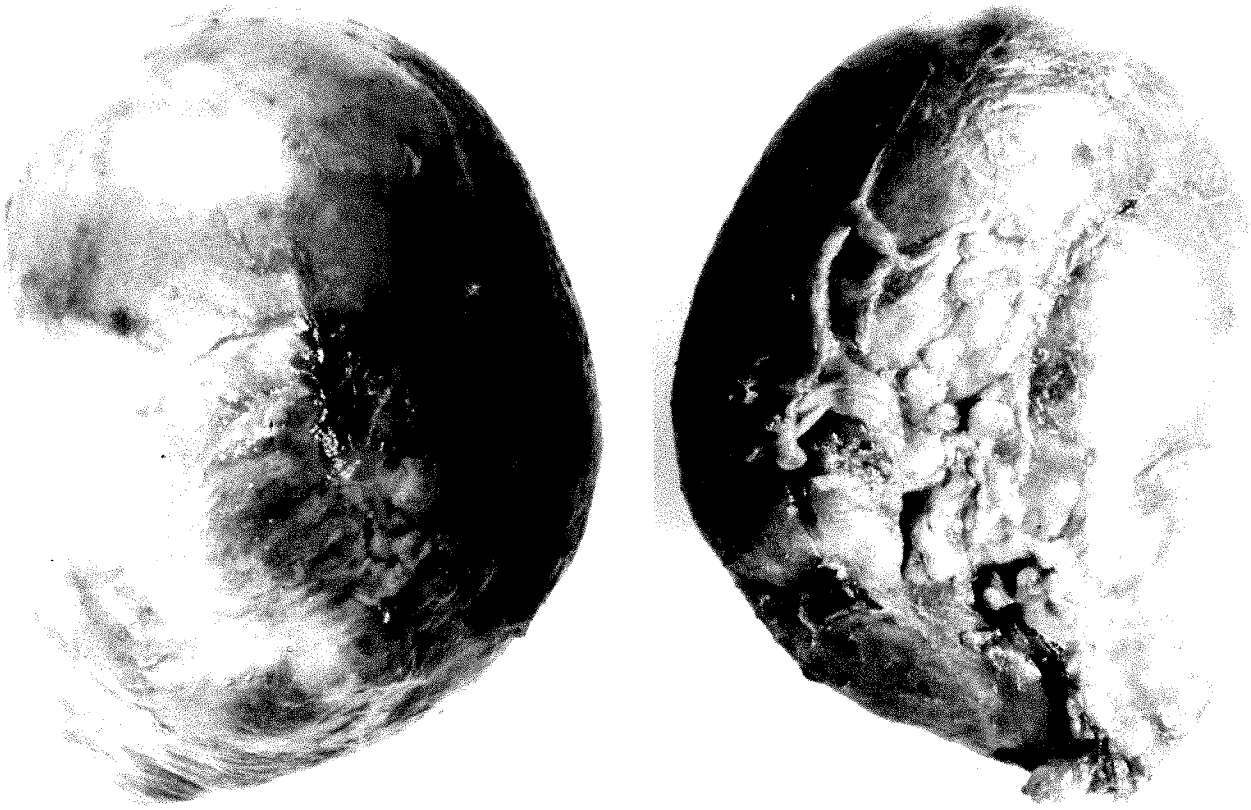

FIG. 2A

FIG. 2B

FIG. 2. Excised specimen (A) Lateral surface. The pseudocyst is located predominantly on the superior and medial aspect of the spleen; (B) Gastric surface. The spleen and the pseudocyst form an unique mass; (C) Bisected specimen. The pseudocyst is unilocular, the inner surface is coated by gray-yellow material.

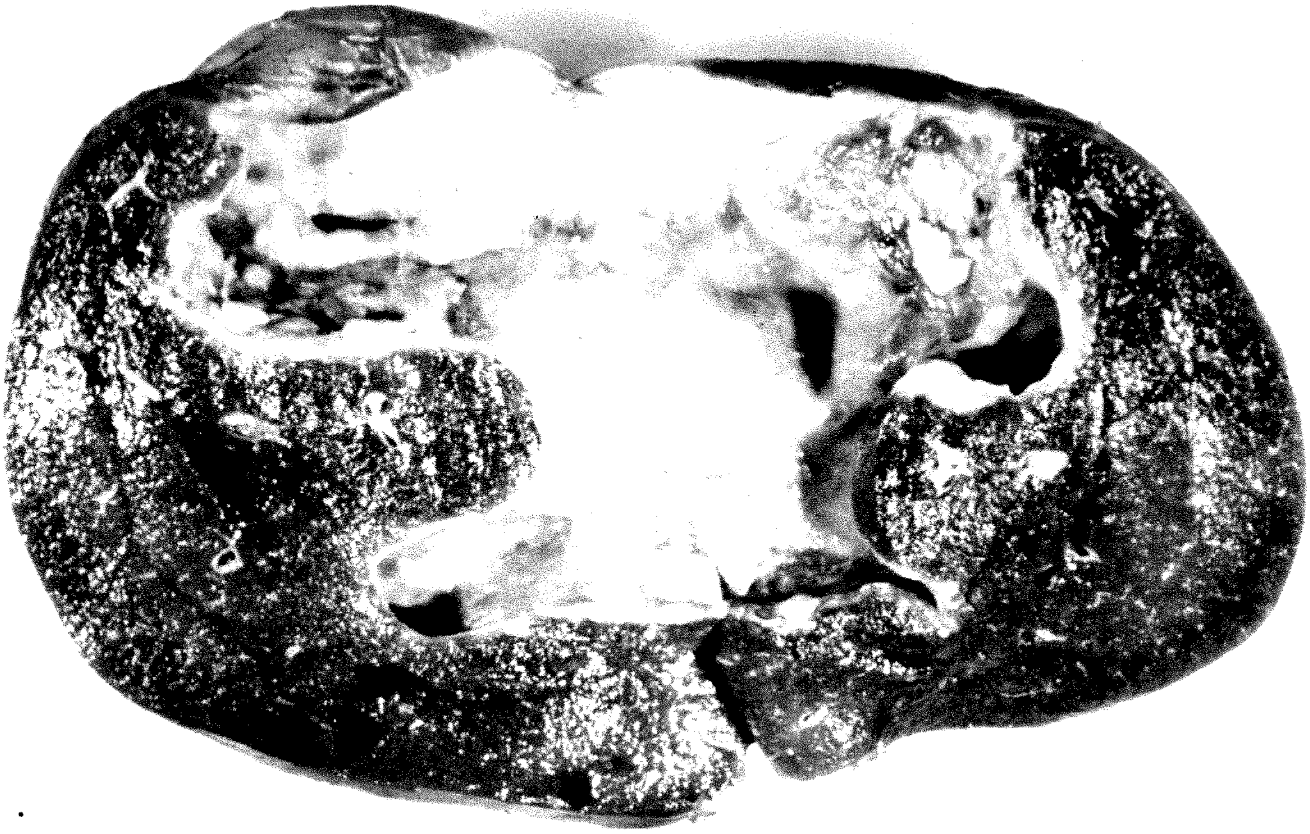

FIG. 2C

was negative. No determination of serum or urine amylase was made.

On October 22 abdominal exploration was undertaken. The spleen was enlarged and adherent to the undersurface of the left diaphragm and to the greater omentum. The pancreas was indurated. Small areas of what was considered fat necrosis were observed beneath the peritoneum close to the tail of the pancreas. The spleen was removed and the abdomen was closed without drainage.

The spleen measured 13 cm × 10 cm × 6 cm. Between the hilum and upper pole there protruded a unilocular cystic lesion, irregular in shape, measuring about 8.5 cm in its greater dimension and containing 250 ml of brown, opaque, thin, and odorless fluid. The inner surface was irregular and coated by adherent gray-yellow amorphous material (Fig. 2). The wall measured up to 4 mm in thickness. Microscopic examination showed the cavity to be lined by fibrous tissue in which there were some lymphocytes. External and adjacent to the wall of the cyst the splenic parenchyma showed coagulation necrosis. In some places within the necrotic area, there were deposits of hemosiderin within phagocytes. Elsewhere in the spleen the capsule was slightly thickened, but the parenchyma was well preserved without evidence of sections of intravescular thrombosis or other significant pathology. The pathologic diagnosis was splenomegaly with a large necrotic lesion, probably a liquefied infarct. Analysis of the intracystic fluid gave the following results: No growth on aerobic and anaerobic culture, amylase concentration 30,000 Somogyi units %, Calcium 22.5 mg %, phosphorus 5.2 mg %, total bilirubin 0.3 mg %, albumin 5.3 mg % and cholesterol 439 mg %.

The postoperative course was uneventful. On the fifth postoperative day the serum amylase was 106 units % (normal 80–200) and the 24-hour urine amylase was <4,500 Somogyi units (normal <8,000). The patient was discharged on the ninth postoperative day. Eight months later he had gained 6.4 kg (14 pounds) in weight and had remained asymptomatic.

Comment

Reports of 7 splenic cysts of pancreatic origin have been found in print.[11,13,16,17] For the purpose of this review a cyst, to be considered intrasplenic, had to have splenic capsule or parenchyma completely surrounding it. It was accepted as pancreatic in origin if intrasplenic pancreatic tissue were demonstrated in or adjacent to the wall of the cyst, the intracystic fluid contained amylase in greater concentration than the serum, or there were preoperative clinical, gross anatomic or preferably microscopic evidence of pancreatitis without a history of recent trauma and no evidence of other primary or secondary disease of the spleen.

The clinical features of the collected cases and the case reported here are listed in Table 1. Six of the 8 patients had documented evidence of pancreatitis. In two of these 6 cases, the splenic pseudocyst was an unsuspected operative finding, and in one of these was associated with pseudocysts of the head and of the tail of the pancreas. One case, in addition to the present one, had no preoperative diagnosis of pancreatitis. This patient had an 8 month history of epigastric pain radiating to the left hypochondrium and weight loss of 14 kg (31 pounds). There was no palpable mass in the left upper quadrant, but splenic enlargement was suggested

TABLE 1. *Pancreatic Pseudocyst of the Spleen*

Author	Age	Clinical Manifestations	Amylase*	Angiography	Scintiscan	Pathology		Treatment
						Pancreas	Splenic Vessels	
Roton	32	Diffuse abdominal pain, wandering enlarged spleen	Preoperative; Serum 60u W	None	None	Pancreatic Heterotopia		Splenectomy
Razemon	60	Weight loss, Epigastric pain radiating posteriorly. LUQ mass. Left pleural effusion	Pleural effusion: 104u W	None	None	Pancreatitis	Thrombosis vein	Splenectomy, caudal pancreatectomy
Razemon	44	15 kg weight loss. LUQ pain radiating to left shoulder, Fever	Preoperative; Urine: 1200u W	None	None	Pancreatitis	Patent	Splenectomy Pancreatectomy
Razemon	32	Epigastric pain radiating posteriorly. LUQ mass, Left pleural effusion, Fever	Preoperative: Serum 32u W, Pleural effusion 512u W	None	None	Pancreatitis		Splenectomy
Linquette	43	14 kg weight loss, epigastric pain radiating to LUQ, vomiting	Preoperative: Serum 64u W	Separation of 2 branches of splenic artery, mass in splenic hilum	None	Pancreatitis	Thromsisbo vein	Subtotal splenectomy, caudal pancreatectomy
Moreau	41	Acute pancreatitis, left pleural effusion	Preoperative: Serum 200–300u S	Cavity on upper pole	None	Pancreatitis	Patent	Splenectomy, caudal pancreatectomy
Moreau	39	Acute pancreatitis	Preoperative: Serum 185–512u S	Cavity on upper pole of the spleen	None	Pancreatic pseudocysts	Patent	Splenectomy, caudal pancreatectomy
Bolivar	47	11 kg weight loss, LUQ pain epigastric soreness, palpable spleen, Fever	Postoperative, Cystic fluid: 3000u S; Serum: 106u S		Cavity upper pole of the spleen	Pancreatitis		Splenectomy

* Normal values for specific laboratory not reported; however usually accepted ranges are as follows:

	Serum	Urine (24 hr)
Wohlgemuth	<10 u	5–20 u
Somogyi	80–120 u	<8000 u

by conventional X-ray studies. Thrombosis of the splenic vein was demonstrated by splenoportography. The intrasplenic location of the lesion was revealed by selective celiac angiography, which showed eccentric displacement of the two main branches of the splenic artery.

Selective angiography was performed in 3 patients. In each instance this study revealed the existence of the lesion. In one of the 7 patients previously reported, the existence of the splenic cyst was discovered accidentally by aspirating brown fluid during percutaneous splenoportography. Three principal mechanisms by which a cyst of pancreatic origin may develop in the spleen have been proposed: 1) cystic changes in pancreatic heterotopia of the spleen;[2] 2) liquefaction of an infarct or hematoma secondary to splenic artery or vein thrombosis in pancreatitis,[3,10,11,16] and 3) direct action upon the intrinsic splenic vessels and parenchyma by pancreatic enzymes in pancreatitis.[5]

The location of aberrant pancreatic tissue in the spleen can be explained embryologically. The tail of the pancreas and the spleen develop contiguously within the dorsal mesogastrium and the 2 organs maintain this close relationship. The lesion has been found in the splenic capsule and within the splenic parenchyma, with an incidence varying from 0.3 to 1.6%[2,7,9,15] of all sites of pancreatic heterotopia reported. Occasionally chronic inflammation, acute necrosis and neoplastic changes have been found in aberrant pancreas.[2]

One instance of a pseudocyst developing in pancreatic tissue located in the spleen has been described.[17]

Pseudocysts may appear subsequent to liquefaction of infarcts of the spleen, most of which result from thrombosis of the splenic artery. This is the most frequent splenic complication of pancreatitis.[8,10,13]

Pseudocysts which have not been preceeded by a splenic infarct or which are not associated with thrombosis of the splenic vessels have an obscure pathogenesis[13,16] An enzymatic mechanism has been proposed.[5] Pancreatic enzymes such as elastase and chymotrypsin may reach the spleen by the lymphatic or venous route, where by erosin of the vessels and lysis of parenchyma, they initiate a pseudocyst. Although apparently not advanced previously, a fourth mechanism would appear to be tenable, namely that the pancreatic enzymes liberated in acute pancreatitis might dissect along the splenic blood vessels to produce intrasplenic necrosis. When equilibrium between the forces producing and resisting progression of the process is needed the connection between the spleen and the pancreas might become tenuous and be overlooked at operation or resolve completely leaving a pseudocyst isolated in the spleen.

The diagnosis of a false cyst of the spleen related to the pancreas is unlikely to be made from clinical findings alone. Problems of diagnosis vary according to whether the coexistent pancreatitis has been recognized. In patients with an established diagnosis of pancreatitis, the presence of a mass in the upper abdomen is most likely to be considered a typical pancreatic pseudocyst. Patients in whom pancreatic disease has not been detected present a more difficult problem in differential diagnosis of an upper left abdominal mass.

Scintiscan of the spleen and selective splenic angiography are the most satisfactory methods of localizing an upper abdominal mass to the spleen and to a lesser extent of suggesting its etiology.[11,13] These procedures provide information which cannot be obtained by other means. Splenic scan is a safe, fast and informative test. It can show a circumscribed area of the spleen where the uptake is diminished due to destruction or displacement of the parenchyma. The finding of the so-called binary spleen has been described as suggestive of pseudocyst.[14] It consists in 2 areas of splenic uptake widely separated by an area of absent uptake corresponding to the pseudocyst. This sign can result also from a congested bi-lobed spleen or duplication of the spleen. True cysts are more likely to show a single area of absent uptake at one pole or the other.[12]

Selective splenic angiography also can reveal the presence of a mass lesion in the spleen and yield some information as to its nature.[15] Cystic lesions appear as avascular areas with the intrasplenic arteries displaced and stretched around the lesion. The main artery and vein are of normal size. In contrast some neoplasms show increased or otherwise abnormal vascularity and dilated primary vessels due to increased blood flow.[1,4]

In the case presented here, the lesion was identified as a pseudocyst histologically and its relationship to the pancreas demonstrated by the high amylase concentration of the intracystic fluid. The possibility of its origin in heterotopic pancreas cannot be substantiated or entirely ruled out due to failure to detect pancreatic tissue in or near its capsule. Gross anatomic findings at operation and retrospective evaluation of the patient's history support the diagnosis of antecedent pancreatitis. Angiography was not performed and thromboembolism of the splenic vessels with liquefaction of a splenic infarct secondary to pancreatitis or valvular heart disease can not be excluded. However, the latter etiology could not explain the amylase content of the cyst in any case and the former only if there were a severe acute pancreatitis at the time of the operation, which there was not. There remain 2 other possible mechanisms for development of the pseudocyst, the vascular or lymphatic spread of pancreatic enzymes or direct extension of peripancreatic necrosis into the spleen. The former would seem to be capable of producing a high amylase concentration in the pseudocyst only during the acute episode of pancreatitis if at all. The latter will achieve this effect if the pseudocyst retained a connection with the pancreas which was small and overlooked at operation or if this connection became obliterated after the cyst was mature and the amylase within the cavity of the cyst were not absorbed. Analysis of this fluid indicates that the wall was selectively permeable.

The final identification of the splenic lesion as a cyst and specifically as a pseudocyst must depend on pathologic study at or after the operation. In at least 1 instance, a pancreatic pseudocyst of the spleen was diagnosed by unplanned aspiration during the performance of an splenoportogram. This is considered too hazardous, however, to recommend as a routine procedure.[6] Histologically, the wall of a pseudocyst lacks an epithelial lining. Usually there is an inflammatory reaction in the fibrous capsule which may contain calcium and cholesterol clefts. The microscopic identification of pancreatic tissue in or adjaecnt to this capsule is strongly indicative of the pancreatic origin of the cyst whether it be true or false cyst. The single most important laboratory test of pancreatic origin is the detection of a high concentration of amylase in the contents of the cyst. However, as in the case of pancreatic pseudocysts in other locations, a normal level of amylase may be encountered and does not preclude the diagnosis.

Summary

To 7 reported instances of intrasplenic pseudocyst due to pancreatic pathology is added that of a 47-year-old man who underwent splenectomy for the erroneous diagnosis of splenic infarct or abscess secondary to subacute bacterial endocarditis of the aortic valve. The true etiology of the lesion might have gone unrecognized had not a determination of amylase concentration been done on the intracystic fluid. This suggests that the true incidence of this complication of pancreatitis might be higher than the sparcity of the reports would indicate. The intrasplenic location of such a lesion is best indicated by celiac angiography or splenic scintiscan. Its pancreatic origin is most reliably indicated by a high amylase concentration of the contained fluid. Treatment of the lesion was splenectomy accompanied as necessary by procedures to relieve obstruction of the pancreatic duct.

References

1. Ahlgren, P.: Splenic Cysts. Dan. Med. Bull., **15**:62, 1968.
2. Barbosa de Castro, J. J., Dockerty, M. B. and Waugh, J. M.: Pancreatic Heterotopia. Surg. Gynec. Obstet., **82**:527, 1946.
3. Byrd, B. F. and Couch, O. A.: Pancreatitis with Rupture of the Spleen and Hemorrhagic Pleural Effusion. JAMA, **159**: 1112, 1955.
4. Bron, K. M. and Hoffman, W. J.: Preoperative Diagnosis of Splenic Cysts. Arch. Surg., **102**:459, 1971.
5. Caroli, J., Julien, C., Chevrel, B., Eteve, J. and Demisleau, J.: Nécrosis hépatosplénique d'origine pancréatique. Colloque de l' Hopital Saint Antoine, Paris, 3 April 1965 by Linquette M, et Al in Pseudo-Kyste Hematique de la Rate it Pancreatite. Lille Med., **11**:1012, 1966.
6. Eban, R. E.: Splenic Cyst with Preoperative Diagnosis. Brit. J. Radiol., **32**:821, 1959.
7. Faust, D. B. and Mudgett, C. L. S.: Aberrant Pancreas with Review of the Literature and Report of a Case. Ann. Intern. Med., **14**:717, 1940.
8. Hoffman, E.: Non Parasitic Cysts of the Spleen. Amer. J. Surg., **93**:765, 1957.
9. Hunt, V. C. and Bonesteel, H. T. S.: Meckel's Diverticulum Containing Aberrant Pancreas. Arch. Surg., **28**:425, 1935.
10. Leger, L.: L'atteinte de la veine splenique au cours et au decours des faux kystes du pancreas. J de Chirurgie, **81**:15, 1961.
11. Linquette, M., Combemale, B., Mesmaque, R., Beghin, B. and VanKemmel, M.: Pseudo kyste hematique de la rate et pancreatitis. Lille Med. **11**:1012, 1966.
12. McNamara, J. J., Murphy, L., Griscom, N. T. and Tefft, M.: Splenic Cysts in Children. Surgery, **64**:487, 1968.
13. Moreau, J. and Bismuth, H.: Les complications spleniques des pancreatities chroniques. Presse Med., **77**:1467, 1969.
14. Pearson, H. A., Toulokian, R. J. and Spencer, R. P.: The Binary Spleen: A Radioisotopic Scan of Splenic Pseudocyst. J. Pediat., **77**:216, 1970.
15. Poppi, A.: Sui pancreas aberranti. Arch. Ital. Mal. Appar. Dig., 4:534, 1935.
16. Razemon, P., Salember, Y., Gautier-Benoit, Cl., Houcke, M. and Thery, Cl.: Kystes hematiques de la rate en relation avec une pancreatite. Presse Med., **73**:2863, 1965.
17. Roton, Mileng and Aubertin: Observation d'un kyste pancreatique de la rate. Rev. Med. Francaise d'Extreme Orient, **19**:139, 1941.

Hepatic Cellular Responses to Liver Cancer:

Abnormalities in Metabolism of Mitochondria Isolated from Human Liver Involved with Carcinoma

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THE SEQUENCE OF CLINICAL EVENTS leading from liver insufficiency to death is recognized as one of the common manifestations of liver cancer. Adequate reserve of liver function is the major factor which influences the survival of pateints. Especially, there is great need for an accurate estimation of hepatic functional reserve in the liver remnant to determine the ability of the patient to survive major hepatic resection without complications and death. This problem has been extensively studied in this laboratory.

While there have been several meticulous studies on abnormalities of liver function tests in patients with liver cancer,[3,17,18,20] there are little quantitative data available concerning the nature of hepatic cellular response to liver cancer. Fisher *et al.*[4] have reported that an alteration of hepatic "soil" induced by liver injury increases the incidence of artificially induced hepatic metastases. However, because of the complex nature of this problem, further biochemical study, at a subcellular level, of liver tissue around tumor seemed necessary to clarify more clearly the biological behavior of human liver cancer.

On the other hand, recent studies from our laboratory showed that an enhancement of mitochondrial metabolism following an increased metabolic load upon liver has the properties of a compensatory event for generation of energy[5,10,11] and plays an important role in maintaining hepatic functional reserve.[12] Patients who had liver mitochondria with cytochrome $a(+a_3)$ content less than 0.5×10^{-10} moles per mg of mitochondrial protein were found to have a high rate of postoperative complication.[13]

Thus, it seemed of interest to clarify the hepatic cellular responses to liver cancer with particular reference to the metabolism of liver mitochondria. In this study, evidence will be presented to show a definite relationship between the grade of liver mitochondrial derangement and the distribution of cancer in the liver. Evaluation of those data would be of great help not only in establishing more rigid criteria for hepatic functional reserve, but in estimating the risk of operation in patients with liver cancer.

Methods

Human biopsy material weighing 0.4–1.5 g from areas of the liver edge was obtained at operation, as reported previously.[14] A biochemical analysis of mitochondrial metabolism was made on 44 biopsy specimens of liver with primary and secondary carcinoma obtained immediately after laparotomy and 1 autopsy specimen from postmortem examination performed within 3 hours after death. Fifteen patients had primary tumor of

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the liver. All other patients had secondary tumors: from the stomach in 20, the colon and rectum in 5, the pancreas in 3, and the gallbladder in 1. The ages of the patients ranged from 27 to 72 years, with a mean of 58 years. There were 30 men and 14 women. For comparison, 19 patients 14 to 47 aged (10 males, 9 females) who had clinically normal liver function and histologically normal findings of biopsy specimens were selected as a control.

Isolation of Liver Mitochondria and Measurement of Oxidative Phosphorylation and Respiratory Enzymes

Liver mitochondria were prepared by the method of Ozawa *et al.*[14] In the liver with tumor of multiple nodule, approximately 0.2 mm thick slices of biopsy specimen were cut with a slicer (Natume, Co. Ltd.) and hepatic tissues were carefully separated by dissection from tumor tissues. Oxygen consumption was measured polarographically with a rotating electrode according to the method previously described.[11] Phosphorylative efficiency was measured simultaneously with oxygen utilization by following the change in pH with glass electrode. For the assay of respiratory enzymes of liver mitochondria, the spectrophotometric techniques are described elsewhere.[14] Protein was determined by the method of Lowry *et al.*[7] with crystalline bovine serum albumin as standard.

Results

The contents of cytochrome $a(+a_3)$ per unit of wet weight of liver and respiratory enzymes per mg of mitochondrial protein, and mitochondrial phosphorylative efficiency in the lobes bearing multiple nodules or extensive massive tumors are shown in Table 1, compared with those of normal liver mitochondria from patients 14 to 47 years of age. The concentration of cytochrome $a(+a_3)$ per unit of wet weight of liver were severely decreased in the mitochondria from the lobe involved with cancer ($p < 0.05$), as far as is concerned with patients biopsied in this study, being more remarkably in secondary cancer than in primary cancer. No significant changes in the concentration of cytochrome $c+c_1$ were demonstrated in the mitochondria from the lobes bearing primary and secondary cancer. However, in the mitochondria from lobes bearing primary cancer, the concentration of cytochrome $a(+a_3)$ per mg of mitochondrial protein was decreased to 78% of controls, while in the mitochondria from lobes bearing secondary cancer those of cytochromes $a(+a_3)$ and b were 55 and 66% respectively. The ratio of cytochrome $c+c_1$ to cytochrome $a(+a_3)$ increased to 1.70 ± 0.22 (mean value ± S.E.) in primary cancer and 2.16 ± 0.24 in secondary cancer compared with 0.94 ± 0.05 of control patients. The phosphorylative efficiency of liver mitochondria was calculated on a basis of mitochondrial protein (absolute activity) and mitochondrial concen-

TABLE 1. *Changes in Concentrations of Respiratory Enzymes and Phosphorylative Efficiency of Liver Mitochondria Isolated from the Lobe with Multiple Nodules or Extensive Massive Tumor*

	Number of Patients	$a(+a_3)$ per g wet wt. (10^{-9} moles)	Respiratory Enzymes						Phosphorylation Rates			
									Glut.		Glut. + Succ	
			$a(+a_3)$	b	$c + c_1$	fp	PN	$c + c_1$/ $a(+a_3)$	phos./ mg**	(TN)P***	phos./mg	(TN)P
			10^{-10} moles/mg protein									
Control	19	4.96 ± 0.13*	0.81 ± 0.02	0.59 ± 0.03	0.76 ± 0.02	5.1 ± 0.4	31 ± 2	0.94 ± 0.05	31.8 ± 2.0	27.5 ± 1.9	41.7 ± 2.6	36.6 ± 2.1
Primary Cancer	15	3.65 ± 0.57	0.62 ± 0.15	0.57 ± 0.12	0.89 ± 0.19	5.7 ± 0.2	38 ± 4	1.70 ± 0.22	23.2 ± 3.7	29.6 ± 3.2	42.6 ± 9.7	37.6 ± 5.0
Secondary Cancer	28	2.08 ± 0.31	0.44 ± 0.05	0.40 ± 0.05	0.83 ± 0.07	3.9 ± 0.7	31 ± 2	2.16 ± 0.24	17.1 ± 6.7	17.4 ± 3.8	29.5 ± 8.8	34.4 ± 8.4

fp, Flavoprotein; PN, Pyridine Nucleotide

* Mean + S. E.

** phos./mg, phosphorylation rate per mg protein (mμmoles ATP synthesis/mg protein/min, at 22°C, pH 7.4)

*** (TN)p, cytochrome $a(+a_3)$-turnover number in phosphorylative capacity (4 × moles of ATP synthesis per mole of cytochrome $a(+a_3)$ per second)

TABLE 2. *Changes in Concentrations of Respiratory Enzymes and Phosphorylative Efficiency of Liver Mitochondria Isolated from the Liver with Multiple Nodules in Both Lobes*

Patient No.	Age Sex		Type of Surgery	Course	$a(+a_3)$ per g wct wt. 10^{-9} moles	Respiratory Enzymes						Phosphorylation Rates			
												Glut.		Glut. + Succ.	
						$a(+a_3)$	b 10^{-10} moles/mg protein	$c + c_1$	fp	PN	$c + c_1$/ $a(+a_3)$	phos./ mg	(TN)P	phos./ mg	(TN)P
1	53 F	hepatoma with cirrhosis	exploration only	died 4 days		0.09		0.23		56	3.0				
2	48 M	hepatoma	exploration only	died 10 days		0.42	0.31	0.54	5.4	56	1.3	14.0	22.0	20.3	32.0
3	64 F	hepatoma	autopsy case			0.22	0.33	>0.62			>2.8				
4	52 M	pancreas cancer	distal pancreatectomy	—		0.30	0.22	0.84	3.7	43	2.8				
5	56 M	gastric cancer	1) lt. hepatectomy 2) subtotal gastrectomy	died 40 days		0.51	0.66	0.98	3.7	19	1.9	14.2	18.5	20.7	27.0
6	62 M	gastric cancer	partial gastrectomy	died 14 days	2.16	0.38	0.51	0.96	5.9	38	2.6				
7	55 M	gastric cancer	Witzel gastrostomy	died 25 days		0.32	0.17	0.73	6.6	63	2.3				
8	65 M	gastric cancer	total gastrectomy	died 20 days	2.70	0.52	0.55	0.58	6.3	34	1.1				
Total cases 8			Mean Value ± S. E.	19 days ± 5	2.43 ± 0.19	0.34 ± 0.04	0.39 ± 0.06	0.69 ± 0.08	5.3 ± 0.4	42 ± 5	2.2 ± 0.2	14.1 ± 0.0	20.3 ± 1.2	20.5 ± 0.1	29.5 ± 1.7
9	60 M	hepatoma	lt. hepatectomy	alive 3 months	5.37	1.45	1.10	1.88	5.97	39	1.3	54.8	25.2	63.3	29.0

See Table 1. for abbreviations

TABLE 3. *Changes in Concentrations of Respiratory Enzymes and Phosphorylative Efficiency*

Patient No.	Age Sex	Primary Disease	Type of Surgery	Course	Lobe with an intermediate amount of tumor						
					$a(+a_3)$ per g wet wt. 10^{-9} moles	Respiratory Enzymes $a(+a_3)$ 10^{-10} moles/mg protein	b	$c + c_1$	fp	PN	$c + c_1/a(+a_3)$
1	57 M	hepatoma	exploration only	died 2 months	3.70	0.85	0.7	1.06	6.1	27	1.20
2	58 F	colonic cancer	exploration only	died 3 months							
3	66 M	colonic cancer	Rt. hemicolectomy	alive 2 months							
4	64 F	gastric cancer	partial gastrectomy	alive 3 months							
5	63 M	gastric cancer	partial gastrectomy	died of serum hepatitis 2 months							
6	72 M	gastric cancer	partial gastrectomy	alive 6 months	3.41	0.79	0.62	0.73	5.2	50	0.93
Total cases 6			Mean value ± S. E.								

* See Table 1 for abbreviations

tration of cytochrome $a(+a_3)$ (cytochrome $a(+a_3)$-turnover number*). In the mitochondria from the lobe bearing primary cancer the absolute activity of phosphorylation with glutamate as a substrate decreased to about 70% of the corresponding value of normal mitochondria but cytochrome $a(+a_3)$-turnover number in phosphorylative capacity was within normal limits. This indicates that the phosphorylation rates of the mitochondria from the lobe bearing primary cancer are decreased by the reduction of the concentration of respiratory enzymes but phosphorylative efficiency of the respiratory assembly consisted of a basic set of respiratory carrier is within normal limits. The phosphorylation rates with glutamate plus succinate as substrates were not inhibited in both absolute activity and cytochrome $a(+a_3)$-turnover number. On the other hand, in the mitochondria from the lobe bearing secondary cancer not only the absolute activity of phosphorylation but cytochrome $a(+a_3)$-turnover capacity with glutamate as a substrate were remarkably decreased to 17.1 ± 6.7 $m\mu$ moles ATP synthesis/mg/min and 17.4 ± 3.8 times/second respectively. With glutamate plus succinate as substrates only the absolute activity of phosphorylation was partially inhibited. Consequently, it is likely that the reduction of phosphorylative capacity of the mitochondria from the lobe with secondary cancer results from both a decrease of respiratory enzymes and loose coupling between phosphorylation and oxidation, as previously reported.[15]

Table 2 shows the contents of respiratory enzymes and phosphorylative efficiency of the mitochondria from hepatic tissues with multiple foci of tumor scattered throughout both lobes. In all cases, 60% or more of the liver was pervaded with tumor tissue. Whatever the type of cancer, the concentration of cytochrome $a(+a_3)$ was less than 0.5×10^{-10} moles per mg of mitochondrial protein and their phosphorylation rates were severely inhibited. Patients with the heaviest involvement of whole liver due to cancer had the shortest longevity following laparotomy. The mean survival for those patients surviving the postoperative days was 19 days (14–40 days). Exceptionally, in patient No. 9, though both lobes of liver were invaded by multiple nodular hepatoma, there was no cirrhosis but marked hypertrophy. The mitochondria from hepatic tissues showed markedly higher amount of respiratory enzymes. The concentrations of cytochromes $a(+a_3)$, b and $c + c_1$ per mg of mitochondrial protein increased to 181%, 187% and 246% respectively in comparison with the corresponding concentrations for the controls. The patient survived left hepatectomy. However, when massive tumor or several nodules were localized in both lobes, but the tumor tissues were presumably less than 20% of the liver, in many cases the concentrations of respiratory enzymes and cytochrome $a(+a_3)$-turnover number in phosphorylative capacity were within normal limits (Table 3). These patients fared relatively better than did those with multiple nodular tumors in both lobes. Consequently, marked mitochondrial derangements were more frequently observed in patients with multiple nodules than in patients with a solitary nodule or mas-

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* Cytochrome $a(+a_3)$-turnover number of phosphorylative capacity: in the steady state phosphorylation these are four times the moles of ATP formed divided by the moles of cytochrome $a(+a_3)$ per second[2].

*of Mitochondria from Liver with Massive Tumor or Several Nodules in Both Lobes**

Phosphorylation Rates Glut. phos./mg	Phosphorylation Rates Glut. (TN)P	Phosphorylation Rates Glut. + Succ. phos./mg	Phosphorylation Rates Glut. + Succ. (TN)P	Lobe with small amount of tumor: Hypertrophy	$a(+a_3)$ per g wet wt. 10^{-9} moles	Respiratory Enzymes $a(+a_3)$ 10^{-10} moles/mg protein	b	$c + c_1$	fp	PN	$c + c_1/a(+a_3)$	Glut. phos./mg	Glut. (TN)P	Glut. + Succ. phos./mg	Glut. + Succ. (TN)P
55.0	43.1	56.0	44.0	(+)	4.20	0.88	0.66	0.98	6.4	30	1.17	56.0	42.7	65.5	50.0
				(−)		0.61	0.56	0.86	4.4	38	1.40				
				(+)		0.69	0.32	0.60	3.1	28	0.88	28.2	27.2	36.0	34.8
				(+)	5.37	1.05	0.83	1.12	7.2	30	1.07	39.4	25.0	44.3	28.1
				(−)		0.88	0.69	1.14	7.6	40	1.30	32.7	25.0	52.2	39.7
30.0	25.5	42.5	36.0												
					4.79 ± 0.41	0.82 ± 0.06	0.61 ± 0.07	0.94 ± 0.08	5.7 ± 0.7	33 ± 2	1.14 ± 0.08	39.1 ± 5.2	30.0 ± 3.7	49.5 ± 5.4	38.2 ± 3.9

sive tumor. In general, the smaller the detectable mass the less likely that the mitochondrial derangement has taken place.

Table 4 shows the concentrations of respiratory enzymes and phosphorylation rates of the mitochondria from hepatic tissues with massive tumor apparently restricted to one lobe. The metabolic changes of the mitochondria from the lobe bearing cancer varied widely in the study group, but a trend to decrease was found in the concentrations of respiratory enzymes and the phosphorylative efficiency of mitochondria. On the contrary, in the other lobe without cancer the concentrations of cytochromes $a(+a_3)$ b and $c + c_1$ were remarkably increased to 147%, 135% and 145% of controls respectively and the absolute activity of mitochondrial phosphorylation was increased to about 160% of controls. Also, macroscopically there was marked hypertrophy. Of these, 5 patients survived the surgical treatment for liver cancer such as hepatic resection and ligation of hepatic artery and a portal vein branch.[6] In view of recent concept of mitochondrial enhancement this finding seems of great interest. The enhancement of mitochondrial metabolism appears to be able to take over the mitochondrial function of the lobe bearing cancer by virtue of oxidative phosphorylation enhanced with the increase of respiratory carriers. Those patients would live more than three months. However, no occurrence of such an enhancement in the lobe without cancer resulted in the relatively early death of the patients. Table 5 shows the results of an analysis of liver mitochondria in such patients. In the lobe without cancer, the contents of cytochromes $a(+a_3)$ and b were decreased 61% and 70% of controls respectively and there was no marked hypertrophy. Of 6 patients, despite their minor operation, 5 patients had relatively short survival following laparotomy.

Discussion

Abnormalities in liver mitochondrial metabolism have been found to occur in patients with a variety of liver disease and to be well reflected by the changes in the concentrations of respiratory enzymes.[12,13] These led to the suggestion that hepatic functional reserve is closely related to the changes of concentrations of respiratory enzymes, and patients with more marked decrease of hepatic functional reserve exhibit greater alteration in the concentrations. During these studies, intuitively it seemed to be biologically meaningful that the mitochondria with cytochrome $a(+a_3)$ concentration less than 0.5×10^{-10} moles per mg protein or the $c + c_1/a(+a_3)$ ratio over 2.0 occurred in 23 patients of 145 patients biopsied (cf. ref. 13, Table 2) and 11 patients of 23 patients had liver cancer. In the mitochondria from hepatic tissues with multiple nodules scattered throughout both lobes, the concentrations of cytochromes $a(+a_3)$ and b except cytochrome $c + c_1$ and their phosphorylative capacities were severely decreased. These results indicate that the synthesis of cytochromes $a(+a_3)$, b and, probably, cytochrome c_1 of liver mitochondria were selectively inhibited by liver cancer. These might be attributed to basic difference in the two system; that is, the formation of cytochromes $a(+a_3)$, b and c_1 is dependent on mitochondrial protein synthesis, whereas cytochrome c is synthesized on extra-mitochondrial cytoplasmic ribosomes.[9]

TABLE 4. *Changes in Concentrations of Respiratory Enzymes and Phosphorylative Efficiency*

					Lobe with Cancer						
Patient No.	Age Sex	Primary Disease	Type of Surgery	Course	$a(+a_3)$ per g wet wt. 10^{-9} moles	Respiratory Enzymes $a(+a_3)$ 10^{-10} moles/mg protein	b	$c + c_1$	fp	PN	$c + c_3/a(+a_3)$
1	68 F	hepatoma with cirrhosis	extirpation of tumor	alive 3 years							
2	43 M	hepatoma	ligation of lt. portal vein	died 7 months	3.37	0.74	0.73	1.26	4.9	28	1.70
3	27 M	hepatoma	extended Rt. hepatectomy	alive 1 year		0.28	0.17	0.57			2.04
4	44 F	hepatoma	ligation of Rt. hepatic artery	alive 3 months							
5	67 M	cholangio-carcinoma	external drainage of galle	died 6 months	2.7	0.40	0.40	0.90	5.2	25	2.25
6	72 M	hepatoma	exploration only	alive 4 months		0.35	0.30	0.72	5.4	30	2.06
7	65 M	colonic cancer	cholecystectomy	died of obstructive jaundice 2 months		0.45	0.42	0.98		25	2.98
8	63 M	gastric cancer	lt. hepatectomy	alive 6 months	5.23	1.08	0.80	1.25	4.2		1.16
Total cases 8				Mean value ± S. E.	3.77 ± 0.61	0.55 ± 0.11	0.47 ± 0.09	0.95 ± 0.10	3.9 ± 0.8	27 ± 1	2.03 ± 0.22

* See Table 1 for abbreviations

In many cases with liver cancer of massive type, it is likely that cancer induces the decreases in the concentrations of respiratory enzymes of the mitochondria in the lobe bearing cancer, resulting in a decrease of phosphorylative efficiency. In the same time, the concentrations of respiratory enzymes in the other lobe without cancer is increased on a compensatory manner. Later, with a persisted overload due to enhanced tumor growth the enhanced mitochondrial metabolism is inhibited in parallel with the decrease of respiratory enzymes, then resulting in death. Whatever the mechanisms might be, the decrease of respiratory enzymes of liver mitochondria from liver bearing malignant tumor raises many interesting questions. The decreases of respiratory enzymes and phosphorylative capacity may be related to malignancy but the mechanism is not clear at present. As far as is concerned with this study, secondary cancers exerted a more depressive effect on the liver mitochondrial metabolism than primary cancers. However, the variability of the results from this study do not permit such a conclusion to be made. Also, of the total 44 patients, 2 patients with hepatoma had liver cirrhosis. The cancer was of multiple nodular type (Pt. No. 1 in Table 2) and of massive type (Pt. No. 1 in Table 4). The former showed the greatest decrease of respiratory enzymes of liver mitochondria and died of hepatic failure on the fourth day after exploration, while the latter showed the slight decrease of cytochromes $a(+a_3)$ and b, and survived 3 years after extirpation of 630 g of hepatoma. Also, of 3 patients with liver cirrhosis not associated with cancer, 2 had normal concentrations of respiratory enzymes of liver mitochondria and 1 marked decrease of respiratory enzymes.† In general, it is likely that cirrhosis has an inhibitory effect on respiratory enzymes of liver mitochondria. However, patients with cirrhosis tested to date are too few to be evaluated and a relationship between the degree of cirrhosis and alterations in mitochondrial metabolism are still under investigation.

It has been reported that the respiratory enzymes of tumor cell are characterized with the decrease of cytochrome $a(+a_3)$ concentration associated with a high ratio of cytochrome $c + c_1$ to cytochrome $a(+a_3)$,[1,8,16] compared to those of normal liver mitochondria. It has been found that in pure cancer cell, the aerobic respiration is very low in comparison with the enormous anaerobic glycolysis.[19] Consequently, as the possible biological behavior of tumor cell to hepatic cells, the results reported herein might indicate that an alteration of hepatic parenchyma around tumor leading to the functional state of depressed aerobic phosphorylation precedes an enhancement of tumor growth and promotes the development of metastases and tumor growth.

Previous studies[5,10,13,15] from our laboratory showed that a humoral factor in portal blood is concerned with an enhancement and depression of mitochondrial metab-

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† Ozawa, K., Unpublished observation.

*of Mitochondria from Liver with Massive Tumor Restricted to One Lobe**

Lobe without Cancer															
Phosphorylation Rates					a(+a_3) per g wet wt.	Respiratory Enzymes						Phosphorylation Rates			
Glut.		Glut. + Succ.										Glut.		Glut. + Succ.	
phos./mg	(TN)P	phos./mg	(TN)P	Hypertrophy	10^{-9} moles	a(+a_3) 10^{-10} moles/mg protein	b	c + c_1	fp	PN	c + c_3/a(+a_3)	phos./mg	(TN)P	phos./mg	(TN)P
				(+)		0.65	0.42	0.96	5.2	14	1.48				
36.2	32.6	60.5	54.6	(+)	6.68	1.36	1.12	1.27	5.5	16	0.94	59.0	29.0	88.7	43.5
				(+)		0.84	0.68	0.87	4.9	35	1.03				
				(+)		1.07	0.62	1.03	6.7	48	0.97	46.5	29.0	65.0	40.4
				(+)	4.47	1.17	0.92	1.12			0.96				
				(+)	5.01	1.11	0.88	1.24	4.9	52	1.11				
0	0	39.3	58.4	(+)		1.00	1.19	1.38	1.2	42	1.38	52.8	35.2	35.8	35.9
32.2	19.9	47.5	29.1	(+)	5.30	1.19	0.55	1.20	6.2	7	1.01	47.8	26.8	69.2	39.0
22.8 ± 9.3	17.5 ± 7.7	49.1 ± 5.0	47.4 ± 7.5		5.37 ± 0.43	1.05 ± 0.07	0.80 ± 0.09	1.13 ± 0.05	5.0 ± 0.6	31 ± 6.30	1.10 ± 0.68	51.5 ± 2.4	30.0 ± 1.6	69.1 ± 6.3	39.7 ± 1.4

olism associated with regeneration and atrophy, and that liver mitochondria with the concentration of cytochrome a(+a_3) less than 0.5 × 10^{-10} moles/mg protein could not respond to energy need by increased metabolic load. Thus, the mitochondria from the lobe bearing cancer, if the cytochrome a(+a_3) concentration is depressed to less than 0.5 × 10^{-10} moles/mg protein, appear to be unable to effectively utilize the humoral factor, resulting in a rise in the levels of available factor to the mitochondria in the lobe without cancer, and then the increase of respiratory enzymes. Consequently, considering that this humoral factor plays an important role in the maintenance of energy balance in liver even in the presence of cancer, the lack or reduction of an ability of mitochondrial to utilize such an available factor may provide the hepatic soil favorable to enhanced tumor growth and the augmentation of hepatic metastases.

Is there any method to predict occurrence of hepatic failure after hepatic resection? The greatest practical importance in demonstrating hepatic functional reserve may be in the evaluation of regenerative capacity of liver that remained after hepatectomy. Recent studies from our laboratory showed that an enhancement of phosphorylative capacity of mitochondria is requisite for regenerating process such as synthesis of nuclear DNA.[5] In view of the inability of human liver mitochondria to significantly induce an enhancement of ATP synthesis capacity, when the concentration of cytochrome a(+a_3) is reduced to less than 0.5 × 10^{-10} moles per mg of mitochondrial protein, it seemed likely that the energy production by those mitochondria is not sufficient to induce liver regeneration and to maintain life. Consequently, it is not unreasonable to accept that, when the concentration of cytochrome a(+a_3) of the mitochondria from remnant liver is less than 0.5 × 10^{-10} moles per mg protein, major hepatic resection should not be performed.

In this department, the measurement of respiratory enzymes and phosphorylative efficiency of the liver which will remain after hepatic resection, have routinely been done prior to contemplated major hepatic resection. In the cases in which the concentrations of respiratory enzymes from remnant liver were within normal limits or more, surgical procedures such as major hepatic resection and ligation of hepatic artery and a portal vein branch have successfully been performed, as seen in Table 4. On the other hand, in the cases in which those were less than 0.5 × 10^{-10} moles per mg protein, such surgical procedures have not been performed, as seen in Table 5. This criterion has been proved to be useful to provide a predictive information for reducing the incidence of postoperative hepatic failure and avoiding operation on liver with seriously compromised regenerative capacity. In addition, in order to prevent irreversible liver damage secondary to chemotherapeutic agents, no chemotherapy has been done in the patients whose cytochrome a(+a_3) concentration of the liver mitochondria from both lobes or the lobe without

TABLE 5. *Changes in Concentrations of Respiratory Enzymes and Phosphorylative Efficiency of*

					Lobe without Cancer						
Patient No.	Age Sex	Primary Disease	Type of Surgery	Course	$a(+a_3)$ per g wet wt. 10^{-9} moles	Respiratory Enzymes $a(+a_3)$ 10^{-10} moles/mg protein	b	$c + c_1$	fp	PN	$c + c_1/a(+a_3)$
1	69 F	hepatoma	exploration only	died 2 months	2.15	0.51	0.39	0.69	6.4	41	1.4
2	57 F	cancer of gall bladder	cholecystectomy	died 2 months							
3	40 F	rectal cancer	formation of jejunal fistula	died 11 days							
4	63 M	gastric cancer	subtotal gastrectomy	died 8 months							
5	57 M	1) gastric cancer 2) cholelithiasis	choledocholithotomy	died 2 days							
6	49 F	gastric cancer	transverse colostomy	died 24 days							
Total cases 6				Mean value ± S. E.							

* See Table 1 for abbreviations

cancer are decreased to less than 0.5×10^{-10} moles per mg of mitochondrial protein. In a subsequent paper, a more detailed study concerning those will be presented.

Summary

To clarify the hepatic cellular responses to liver cancer, a biochemical analysis of liver mitochondrial metabolism was made on 44 biopsy specimens of liver with primary and secondary cancer.

In the mitochondria from hepatic tissues with multiple nodules scattered throughout both lobes, the concentrations of cytochromes $a(+a_3)$ and b were decreased to less than about 50% of controls and their phosphorylation rates were severely inhibited. The mean survival for those patients surviving the postoperative days was 19 days. On the other hand, in hepatic tissues with massive tumor restricted to one lobe the concentrations of respiratory enzymes and the phosphorylation rates of the mitochondria from the lobe bearing cancer were decreased, while those of the mitochondria from the lobe without cancer were remarkably increased in a compensatory manner. Those patients lived more than 3 months. However, when such an increase in the lobe without cancer could not be demonstrated, those patients had relatively short survival.

From the results, it has been suggested that an alteration of hepatic parenchyma around tumor leading to the functional state of depressed aerobic phosphorylation precedes an enhancement of tumor growth and may provide the hepatic soil favorable to enhanced tumor growth and the augmentation of hepatic metastases.

References

1. Chance, B. and Hess, B.: Metabolic Control Mechanism. I. Electron Transfer in the Mammalian Cell. J. Biol. Chem., **234**:2404, 1959.
2. Chance, B. and Hagihara, B.: Direct Spectroscopic Measurements of Interaction of Components of the Respiratory Chain with ATP, ADP, Phosphate, and Uncoupling Agents. p. 1. Intracellular Respiration (Fifth International Congress of Biochemistry, Moscow, 1961), vol. 25. London, Pergamon Press, 1963.
3. Fenster, L. F. and Klatskin, G.: Manifestations of Metastatic Tumors of the Liver. Amer. J. Med., **31**:238, 1961.
4. Fisher, B. and Fisher, E. R.: Experimental Studies of Factors Influencing Hepatic Metastases. III. Effect of Surgical Trauma with Special Reference to Liver Injury. Ann. Surg., **150**:731, 1959.
5. Honjo, I., Ozawa, K. and Takasan, H.: Liver Regeneration and Mitochondrial Metabolism (Presence of a Mitochondria-Stimulating Factor in Portal Blood: Its Relation to Regeneration and Atrophy) *In* Liver Cell Regeneration. R. Molimard, editor. 143, 1972.
6. Honjo, I., Ozawa, K., Suzuki, T. and Takasan, H.: Experimental and Clinical Studies on Ligation of Right or Left Branch of the Portal Vein as a Treatment of Liver Cancer. 9th International Congress of Gastro-enterology, Paris, **1**: 323, 1972.
7. Lowry, O. H., Rosebrough, N. J., Farr, A. L. and Randall, R. J.: Protein Measurement with Folin Phenol Reagent. J. Biol. Chem., **193**:265, 1951.
8. Monier, R., Zajdela, F., Chaix, P. and Petit, J. F.: Low Temperature Spectrographic Study of the Cytochromes in Various Rat and Mouse Tumors. Cancer Res., **19**:927, 1959.
9. Roodyn, D. B. and Wilkie, D.: The Biogenesis of Mitochondria. London, Methuen, 1968.
10. Ozawa, K., Kitamura, O., Yamaoka, Y., Mizukami, T., Kamano, T., Takeda, H., Takasan, H. and Honjo, I.: Role of Portal Blood on the Enhancement of Liver Mitochondrial Metabolism. Amer. J. Surg., **124**:16, 1972.

*Mitochondria from Liver with Massive Tumor Restricted to One Lobe**

					Lobe with Cancer										
Phosphorylation Rates					a(+a₃) per g wet wt. 10^{-9} moles	Respiratory Enzymes			fp	PN	c + c₁/ a(+a₃)	Phosphorylation Rates			
Glut phos./ mg	(TN)P	Glut. + Succ. phos./ mg	(TN)P	Hyper-trophy		a(+a₃) 10^{-10} moles/mg protein	b	c + c₁				Glut. phos./ mg	(TN)P	Glut. + Succ. phos./ mg	(TN)P
21.8	38.5	26.4	34.6	(−)	3.75	0.56	0.42	0.56	5.6	36	1.0	31.0	37.0	37.1	44.0
				(−)		0.42	0.40	0.54	4.3	27	1.3				
				(−)		0.62	0.36	1.27	1.6	37	2.1	6.3	7.5	24.5	26.6
				(−)		0.25	0.32	0.80	5.1	28	3.2				
				atrophic	2.27	0.57	0.57	0.85			1.5	17.4	20.2	35.2	41.2
				(−)		0.54	0.40	0.90	4.4	81	1.7	22.2	27.5	56.6	70.0
					3.01 ± 0.52	0.49 ± 0.05	0.41 ± 0.03	0.82 ± 0.09	4.2 ± 0.6	35 ± 9	1.8 ± 0.3	19.2 ± 4.4	23.0 ± 5.3	38.4 ± 5.7	45.5 ± 7.8

11. Ozawa, K., Takasan, H., Kitamura, O., Mizukami, T., Kamano, T., Takeda, H., Ohsawa, T., Murata, T. and Honjo I.: Effect of Ligation of Portal Vein on Liver Mitochondrial Metabolism. J. Biochem. 70:755, 1971.
12. Ozawa, K., Takasan, H., Kitamura, O., Yamaoka, Y., Mizukami, T., Kamano, T., Takeda, H. and Honjo, I.: Alteration in Liver Mitochondrial Metabolism in a Patient with Biliary Obstruction Due to Liver Carcinoma. Amer. J. Surg. (In press.)
13. Ozawa, K., Kitamura, O., Yamaoka, Y., Mizukami, T., Takeda, H., Takasan, H. and Honjo, I.: Quantitative Analysis of Respiratory Enzymes of Mitochondria Isolated from Liver Tissue of Patients. J. Lab. Clin. Med. 81:379, 1973.
14. Ozawa, K., Kitamura, O., Mizukami, T., Yamaoka, Y., Kamano, T., Takeda, H., Takasan, H. and Honjo, I.: Human Liver Mitochondria. Clin. Chim. Acta, 38:385, 1972.
15. Ozawa, K., Kitamura, O., Yamaoka, Y., Mizukami, T., Kamano, T., Takeda, H., Takasan, H. and Honjo, I.: Phosphorylative Capacity of Liver Mitochondria of Patients: Its Relation to Cytochrome a(+a₃) Content. Amer. J. Surg. (In press.)
16. Sato, N. and Hagihara, B.: Spectrophotometric Analyses of Cytochromes in Ascites Hepatomas of Rats and Mice. Cancer Res., 30:2061, 1970.
17. Schaefer, J. and Schiff, L.: Liver Function Tests in Metastatic Tumor of the Liver; Study of 100 Cases. Gastroenterology, 49:360, 1965.
18. Viranuvatti, V., Plengvanit, U. and Kalayasiri, C.: Needle Liver Biopsy with Particular Reference to Complications. Amer. J. Gastroent., 42:529, 1964.
19. Warburg, O.: On Respiratory Impairment in Cancer Cells. Science, 124:269, 1956.
20. Yesner, R. and Conn, H. O.: Liver Function Tests and Needle Biopsy in the Diagnosis of Metastatic Cancer of the Liver. Ann. Intern. Med., 59:62, 1963.

Potentiation of Solid-tumor Chemotherapy by Metabolic Alteration

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PROSPECTS FOR IMPROVED CONTROL of human cancers by excision or irradiation are limited by the requirement that the disease be at least regionally localized. Conversely, the prospects for systemic therapy have improved remarkably in the last decade with the demonstration of five to ten year unmaintained remissions in certain tumors after intensive chemotherapy.[35] Curative potential at present is limited largely to lymphomas and childhood malignancies, plus gestational choriocarcinoma; systemic therapy of the common solid tumors of adults generally lacks curative potential and has remained much less promising. Real improvement in this area will probably depend on the development of new agents, or of new approaches to therapy with present agents; either case is likely to require exploitation of biochemical or metabolic differences between malignant and normal tissues.

At present, the most prominent known difference is the disproportionate reliance of the tumor cell on aerobic as well as anaerobic glycolysis in its carbohydrate energy metabolism.[8,9,32] Significant aerobic glycolysis (in excess of oxidation) is a rarity in normal adult tissues; unfortunately, it is not unique to malignant tissues but is shared to a degree by, for example, intestinal mucosa, myeloid bone marrow, and renal medulla. Remarkably, these tissues tend to be those most affected by systemic toxicity of virtually all the commonly used chemotherapeutic agents.

Animal studies suggest that the free-living ascites tumor cell derives about 50% of its energy from glycolysis, as opposed to respiration.[1] ("Respiration" is used in this context in its biochemical sense, denoting oxidative metabolism of carbohydrate substrates via the tricarboxylic acid cycle.) Solid tumors probably derive 15–40% of their energy from glycolysis; even this figure shows a large relative dependence on glycolysis, considering that the complete metabolism of one mole of glucose to water and CO_2 yields a net of only 2 moles of ATP from glycolysis but thirty-six moles from oxidative metabolism.

Malignant cells are known to possess the full complement of respiratory enzymes, and oxidative metabolism in tumors is not qualitatively different from that in normal tissues.[4,34] A number of studies suggest, however, that oxidative metabolism by tumor mitochondria is quantitatively limited, and appears to proceed at a relatively fixed rate under most circumstances.[10,27] To varying degrees, but apparently in rough correlation with the degree of malignancy, tumor tissue appears to escape from normal homeostatic controls over the rate of glycolysis.[2,5]

The result of net preponderance of glycolysis over respiration in a tissue is the accumulation of lactic acid; one aspect of tumor parasitism is its reliance on the host to dispose of excess lactate. Numerous studies have shown tumor pH to be markedly lower than normal tissues.[12,15,17,25,31] Obviously, what is being measured here is tumor interstitial-fluid pH, but the conclusion is inescapable that tumor intracellular pH must also be lower than that of normal tissues. Kahler and Robertson[17] found a tumor pH around 7.0 in fasted animals; a large dose of glucose caused a marked drop in tumor pH but no change in normal tissues. Values of pH below about 6.4 in rat tumors and 6.2 in mouse tumors could not be obtained. This point is of particular interest since Warburg[33] had previously shown that *in vitro* glycolysis was progressively inhibited by falling pH, and was inhibited com-

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pletely at about pH 6.0. The possibility is suggested that in the presence of adequate substrate, tumor energy metabolism may be restricted by the ability of the host to dispose of excess lactate.

There is an additional point in these theoretic considerations. A number of investigators have found that certain rapidly growing transplantable tumors do not oxidize carbohydrate substrates *in vivo.*, but that slices or cell suspensions of these tumors oxidize readily in buffered media.[6,26] The optimal pH *in vitro* for the tricarboxylic acid cycle reactions is about 7.4; it has been suggested that oxidative metabolism in these tumors is inhibited by the low pH.[6,22,28]

If these conclusions are accepted, the question arises whether this feature of tumor energy metabolism can be exploited in systemic therapy; to date at least, it has not been. *A priori* there appear to be 2 possible means by which the Kahler-Robertson effect could be intensified or prolonged in experimental animals: by the production of moderate systemic hypoxemia in the host, or by provision of a continuous high glucose load. The objective of both approaches would be to accentuate the normal relative acidosis of tumor tissue as compared with normal tissue; in this state tumor energy metabolism might be handicapped, and the tumor cells might be made more susceptible to systemic chemotherapy.

A number of investigators have demonstrated reduced tumor growth[3,7] or even regression[30] with animals kept in low oxygen pressure chambers. Marked body weight loss was generally found in these experiments.

Materials and Methods

Reproduceability in an experimental host–tumor system practically requires a transplantable tumor; hence, small animals as hosts. The Walker 256 carcinosarcoma of rats is the best predictor of the clinical effectiveness of chemotherapy among transplanted solid tumors.[14] The measurement of systemic arterial oxygen saturation would, ideally, require larger animals as experimental subjects; the present experiments are handicapped by this problem. The first 2 considerations, however, necessitated choice of rats bearing the Walker tumor for the initial study.

Systemic desaturation by low pressure chambers was not used because of the probability of resultant hypocapnia which might interfere with the desired acidotic effect.[16] Intracardiac or pulmonary right-to-left shunts appeared ideal, but after prolonged trial, were found to be technically impossible in small animals. A surgically created ventilation perfusion imbalance appeared to be a possible alternative; ligation of a main bronchus was tried but abandoned because its effects were very transitory.

A procedure was eventually developed with an acceptably low mortality. Rats were anesthetized with intraperitoneal chloral hydrate (300 mg/Kg), the trachea intubated, and ventilation begun with a Harvard Model 680 rodent respirator.* Left thoracotomy was performed through the 4th or 5th intercostal space using clean but nonsterile technique. The right pulmonary artery was ligated and the left phrenic nerve was divided. Two days later, under light anesthesia supplemented by local infiltration, the right phrenic nerve also was selectively divided in the neck. Total operative mortality was approximately 20% and due to three causes: overdosage of anesthetic; intraabdominal hemorrhage occasioned by the anesthetic injection; and occasionally, inadvertent injury to the pulmonary artery.

The actual degree of systemic arterial desaturation proved almost impossible to determine. Since the defect amounted to a mechanical handicap to ventilation, arterial blood samples could not be drawn without again anesthetizing the animals; anesthesia would accentuate the mechanical handicap, while mechanically assisted ventilation would largely abolish it. Blood samples could be drawn from unanesthetized animals by percutaneous cardiac puncture; but right ventricular admixture in these samples can not be ruled out. In a few animals, lightly re-anesthetized 3 hours after operation and having samples drawn from the abdominal aorta, pO_2 averaged 92 mm as compared with 97–98 mm for controls. These are not presented as valid determinations. The first experiment (study of the effect of desaturation on tumor growth) is severely handicapped by lack of knowledge of the degree of desaturation; but recognizing this defect, it was still felt worth while to complete the experiment. If results appeared significant, the degree of desaturation could later be studied in larger animals.

The second approach, provision of a high continuous glucose load, was studied together with systemic chemotherapy: high-dosage methotrexate (MTX), many times a fatal dose, with subsequent doses of citrovorum factor (CF) for 2½–3 days.[11,20,21] MTX produces a largely irreversible inactivation of intracellular dihydrofolate reductase (DFR), an inhibition completely bypassed by the antidote folinic acid or "citrovorum factor" (n-5-formyl-tetrahydrofolic acid).[13] Whether MTX enters the cell by diffusion or active transport is in doubt. Some investigators have favored a transport mechanism and concluded that transport is somewhat inadequate; if improved entry of MTX into the cell could be provided, a more complete therapeutic result might be obtained.[18] Djerassi,[11] however, attributes the improved therapeutic advantage of high-dosage MTX to increased diffusion into the cell following the C × T principle. The possibility exists of increased MTX diffusion into cells under conditions of accentuated tumor acidosis.

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* Harvard Apparatus Company, Inc., Millis, Massachusetts 02054.

TABLE 1. *Ventilation-Perfusion Defect and Tumor Growth* (Figures given as group mean ± one standard error.)

	Control Group (n = 26)	Experimental Group (n = 23)	p.
A. Mean Tumor Diameter, Day 7	13.2 mm (±0.62)	12.1 mm (±0.42)	*
B. Growth Index,** Days 7–11	247.6 (±5.9)	240.9 (±7.1)	*
Days 11–14	133.2 (±7.0)	−24.5 (±5.6)	<0.001
Days 14–21	165.8 (±7.2)	119.6 (±12.0)	<0.01
C. Percent Body Weight Change (minus tumor), Days 0–21	+8.7 (±1.56)	−16.7 (±1.28)	<0.001

* Difference not significant
** 1000 (Δ log D) for the period.

The principal theoretic considerations in choice of the agent, then, are the following. 1) There is the possibility of giving progressively higher doses of MTX at each treatment. 2) Toxicity can be controlled after each dose by appropriate dosage of CF. 3) If tumor cell replication is reduced even transiently by hypoxemia, fewer tumor cells will be entering S-phase during the time necessary to control bone marrow and intestinal toxicity by CF administration. Methotrexate bound to intracellular DFR then would not exert its effect until the cells do enter S-phase. Hence, a "splitting" of growth dynamics between tumor cells on one hand and bone marrow and intestinal mucosa on the other, might offer a marked increase in therapeutic advantage.

Young adult female CFE strain rats[*] weighing 185–200 grams were used as hosts. Tumors were transplanted weekly under careful sterile precautions, from 2-week old donor tumors. Recipient animals were anesthetized with intraperitoneal chloral hydrate, the right flank closely clipped, and each animal was injected with 0.25 cc of a heavy suspension of tumor cells in saline subcutaneously in the right flank. Cell suspensions were not counted, since tumor growth rate between measurements was to be recorded rather than absolute size. Tails were tattooed with India ink for identification. On the specified days, all animals were briefly anesthetized with ether, and the tumors were measured in three diameters with a small caliper. The mean of the 3 measurements was taken as the tumor diameter. First measurement in both experiments was made on the seventh day; mean tumor diameter averaged somewhat over 1 cm at this time. During appropriate periods after first measurement, tumor growth rate was calculated by the formula (Δ log D)/t, an accurate index to the coefficient of volume expansion with time.[23] Since periods between measurements of experimental and control groups were equal, time was disregarded. The mantissa of common logarithms was read to the third digit and the decimal point disregarded; the actual formula, then, is 1000 (Δ log D) for the time interval. Inspection of this formula will show that tumor regression will be represented by a negative number; volume doubling by a figure of +100, while a figure of +300 indicates three doublings and an eight-fold volume increase. In the common present day usage, a "one-log" increase in cells (or volume) is represented by a change of +333, a "two-log" increase by +667, and a "three-log" increase or decrease by plus or minus 1000.

Experiment I: Ventilation-Perfusion Defect and Tumor Growth

Tumors were inoculated as outlined above. All tumors were first measured on Day 7 after inoculation; any animals bearing tumors too small to measure or definitely under 1.0 cm in mean diameter were discarded. Beginning on Day 7, all animals were maintained on a special high-carbohydrate diet (see footnote, Experiment II). All tumors were measured again on Day 11 and growth index calculated. Also on Day 11, 3 or 4 animals from each transplant generation underwent the surgical procedure outlined above, ligation of the right pulmonary artery and division of the left phrenic nerve. No antibiotics or other medications were given. Two days later, on Day 13, the same animals underwent selective division of the right phrenic nerve in the neck. All tumors were again measured on Day 14 and on Day 21, and the growth index for each interval calculated. A few animals whose tumors ruptured and evacuated before Day 21 (all were controls) were discarded from the series, since tumors could not be measured on Day 21.

Findings are shown in Table 1. Mean tumor diameter at first measurement (Day 7) and tumor growth index between Days 7–11 did not differ significantly between control and operated groups. Growth index for the period of Days 11–14, however, showed moderate regression in the operated animals and continued growth in the controls. The value of t necessary to give a probability of 0.001 that these 2 groups are alike is about 3.8; the actual value of t between the groups is slightly over 17.

The difference in growth index between groups, Days 14–21, though calculated to be significant at the 1% level, may be unacceptable to the reader on the grounds that the tumors were not comparable in size on Day 14. Acceptance is not critical since the important point is the difference in growth rates, Days 11–14.

Intensive chemotherapy during the immediate perioperative period, Days 11–14, was highly toxic and uniformly caused death of the operated animals. Sepsis may have been a factor since the operative procedures were not sterile. The test of chemotherapy was therefore reserved for Experiment II.

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[*] Carworth Farms, New City, New York 10956.

Experiment II: High Glucose Diet and Chemotherapy

Transplant generations were inoculated as in the previous study. On Day 4 after transplantation, one cage of animals was shifted to a special high carbohydrate diet,* ad libitum, while the remaining animals were continued as before on standard laboratory chow.† All tumors were measured on Day 7, and any tumors with less than 1.0 cm mean diameter were discarded. All remaining animals maintained on high carbohydrate diet, and a similar group which had received standard chow, were given MTX 12.5 mg (approximately 60 mg/Kg) subcutaneously. Control animals received no MTX and were continued on standard chow. Both groups of treated animals were given CF in a dose of 0.6 mg, 2 hours after MTX; 0.9 mg that evening; 0.6 mg twice on the next day, and 0.6 mg once on the second day after MTX.

A few treated animals which showed toxicity in the form of mucoid diarrhea on the third or fourth day after the first dose of MTX were discarded, since they tended to develop fatal toxicity after the second dose of MTX.

On Day 12 after inoculation, all tumors were again measured; diets were maintained as before. Previously treated animals were given MTX 25 mg (about 120 mg/Kg), CF 0.6 mg, and benzathine penicillin 15,000 units concurrently. CF was repeated at the same dose 2–3 hours later; 0.9 mg that evening and the next morning, and 0.6 mg twice daily for 3 additional doses, three days in all.

Penicillin was found necessary because, after the second treatment, some animals developed phlegmonous infections of the feet and generally died. These infections clearly originated from avulsed claws, a familiar and generally insignificant injury in most studies involving rats.

Maximum tumor regression had occurred by Day 16 (4 days after the second dose of MTX) and between Days 16–17 very rapid re-growth was apparent. All tumors were again measured on Day 17, and the high carbohydrate diet was discontinued. All animals were kept until Day 21 (9 days after the last dose of MTX) to ascertain that they did not die of delayed toxicity. With the reservations outlined above (dropping of animals which showed intestinal toxicity after the first treatment, and administration of benzathine penicillin at the second treatment), 1 animal out of 30 in Group 3 died. No animals in Group 2 died. Intestinal toxicity seldom if ever occurred following the second treatment. Foot infections did not occur after the first treatment, nor after the second if penicillin was given.

TABLE 2. *High Glucose Diet and Chemotherapy*
(Figures given as group mean ± one standard error.)

	Group 1. Controls Regular Diet (n = 30)	Group 2. MTX − CF Regular Diet (n = 30)	Group 3. MTX − CF Hi-CHO Diet (n = 30)
A. Mean Tumor Diameter, Day 7	12.4 mm ± .23	12.3 mm ± .24	12.2 mm ± .17
		(No significant difference)	
B. Tumor Growth Index,* Days 7–17	548.3 ±7.6	298.5 ±9.0	72.1 ±12.7
p (Groups 1 + 2)	<0.001		
p (Groups 2 + 3)		<0.001	

* Calculated as 1000 (Δ log D), Days 7–17

The results are summarized in Table 2. Tumor size at initial measurement on Day 7 does not differ between groups. From Days 7–17 the animals given a high carbohydrate diet plus MTX-CF showed a tumor growth amounting to less than one volume doubling. Group 2, animals given a regular diet plus MTX-CF, showed approximately three volume doublings, or roughly eight-fold volume increase. Control animals showed over 5 doublings, or a volume increase of over forty-fold. Comparison of Groups 2 and 3, and Groups 1 and 2, again showed a probability of far less than 0.001 that the groups were alike.

Discussion

It seems possible to conclude from these experiments that a dietary intake containing approximately 80% glucose makes transplanted tumors more susceptible to chemotherapy in the form of high-dosage methotrexate with citrovorum "rescue." The response to chemotherapy is highly significant when compared with the same therapy given to animals on a standard diet, containing approximately 50% carbohydrate of all types. Toxicity encountered in these experiments is well below the LD_{10} level considered acceptable for animal studies.

There are a number of practical difficulties in the use of this chemotherapeutic approach with rapidly growing transplantable tumors. Maximum tumor regression was apparent by the 4th day at the latest after each dose of MTX, and rapid regrowth was apparent beginning on or before the 4th day. A 5-day interval between very large doses of MTX (60 and then 120 mg/Kg.) is very short to allow recovery from any toxicity following the first dose. The doubling time of untreated Walker tumors during Days 7–11 may be noted from Table 1 to be slightly under 2 days; on the other hand, very few human tumors show doubling times under about 3 weeks.[24,29] Djerassi *et al.*[11] and Levitt *et al.*,[20] in treating human tumors with high dosage MTX-CF, spaced the treatments at intervals of 2–3 weeks, with subsequent treatments being deferred if necessary until full recovery from any toxicity following the previous dose. Djerassi noted that intervals longer than 3 weeks between treatments were generally associated with rapid regrowth of the tumor.

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* Nutritional Biochemicals Corporation, Cleveland, Ohio 44128. 79% glucose; 15% casein; 4% salt mixture USP; 2% vitamin supplement.

† Purina Formulab, Ralston Purina Company, St. Louis, Missouri 63188. Approximately 50% carbohydrate of all types: corn meal, soybean meal, ground oats, and sucrose.

The rapid growth rate of transplantable small animal tumors is a handicap to the study; still, 2 doses with an interval of 5 days were possible without excessive toxicity. The basic scheme of evaluating chemotherapy protocols, percent tumor weight inhibition in treated animals as compared to controls (TWI T/C), was paralleled in this study. The values actually measured were initial tumor diameter (no difference) and volume growth rate index during the period of treatment, a more rational evaluation than comparison of absolute size.

Blood glucose levels are ordinarily fairly stable in normal individuals. The question therefore arises whether, in order to obtain maximal tumor pH reduction under normally aerobic conditions, it is necessary to provide a large excess of glucose intake, since glucose is also available from the host's glycogen stores and by gluconeogenesis. Gullino *et al.*[15] found glucose levels in tumor interstitial fluid near zero, with low pH and high lactate levels compared with blood. A very tentative answer to the above question might then be yes, since it seems clear that cells of a solid tumor quickly exhaust the glucose normally available in the interstitial fluid. An additional factor controlling pH may be the vascularity of the tumor and consequently the ability of the host both to provide sufficient glucose and to clear lactate from the tumor interstitial fluid.

The second conclusion is that an operative procedure designed to produce ventilation-perfusion imbalance and hence some degree of systemic arterial desaturation, when combined with a high-carbohydrate diet, caused a highly significant reduction in tumor growth rate. Control animals, also on a high carbohydrate diet, showed continuing tumor growth throughout, but in accordance with the Gompertzian growth curve of transplanted tumors.[19] Unfortunately the degree of arterial desaturation, critical to interpretation of this study, was not successfully measured. The surgically produced defect amounted to a mechanical handicap to ventilation; by close observation, the animals appeared to compensate by means of increased respiratory effort during the third week. Whether because of the increased work of breathing or because of an effect of hypoxemia on metabolic processes, the operated animals showed marked weight loss post-operatively. Similar weight loss has been noted in animals kept in low pO_2 chambers;[3,7] these also entail greatly increased respiratory effort.

During the immediate peri-operative period, when moderate tumor regression occurred, intensive chemotherapy was far more toxic to operated animals than to controls. Again, this may have been the result of sepsis, or of increased susceptibility of all hypoxic tissues to methotrexate toxicity. Hypoxemia is known to increase the replication rate of erythroid bone marrow cells through the erythropoietin mechanism; whether any comparable mechanism affects cells of the myeloid series, or of intestinal mucosa, is not established.

Finally, the possibility is suggested that if a stable right-to-left cardiovascular shunt were produced in larger animals, and chemotherapy delayed somewhat to avoid postoperative sepsis, a splitting of growth rates between tumor cells on the one hand and bone marrow and intestinal mucosa on the other, might offer a marked improvement in therapeutic advantage. In this circumstance, a rational chemotherapy protocol could include use of a complete antidote early, to permit sparing of the much more rapidly replicating cells of the bone marrow and intestinal mucosa, while the primary agent had a later effect on tumor cells. The combination of high-dosage methotrexate with citrovorum "rescue" seems to fit these criteria. The agents have been found suitable for prolonged clinical administration at three week intervals,[11] with resultant gradual continuing tumor regression in patients whose arterial oxygen saturations were presumably unaltered.

If clinical application of such a program ever becomes feasible, it is quite obvious that many cancer patients could not tolerate the added stress of a right-to-left shunt. The findings suggest also that a better tumor response might be obtainable by a program of glucose hyperalimentation plus MTX-CF chemotherapy than by chemotherapy alone.

Summary

Observations dating back many years have established the existence of significant excess aerobic glycolysis in tumor tissue. Not quite unique to tumor tissue, this characteristic is shared to a degree by those normal body tissues which tend to be most susceptible to systemic toxicity of many commonly used anticancer drugs.

Excess glycolysis results in lactate accumulation and a fall in tumor interstitial fluid pH to levels remarkably low for living tissue. The lowest attainable level of tumor pH seems to be controlled by the inhibition of glycolysis as pH approaches 6.0.

The above mentioned studies suggested the possibility that under induced conditions, tumor energy metabolism might be restricted by low pH levels, and that tumor cells might thus be made more susceptible to systemic chemotherapy. Experimental results reported here do not contradict this thesis, and may be interpreted as lending it tentative support. Observed effects on transplanted tumors were highly significant when compared to controls.

References

1. Aisenberg, A. C.: The Glycolysis and Respiration of Tumors. New York, Academic Press, 1961.

2. Auersperg, N.: Histogenetic Behavior of Tumors. III. Possible Relationships to Patterns of Glycolysis. J. Nat. Canc. Inst., **48**:1589, 1972.

3. Barach, A. L. and Bickerman, H. A.: The Effect of Anoxia on Tumor Growth with Special Reference to Sarcoma 180 Implanted in C57 Mice. Canc. Res., **14**:672, 1954.

4. Barbon, S. and Schulze, H. O.: Metabolism of Tissue Culture Cells. The Presence in HeLa Cells of the Enzymes of the Citric Acid Cycle. J. Biol. Chem., **22**:665, 1956.

5. Burk, D., Woods, M. and Hunter, J.: On the Significance of Glucolysis for Cancer Growth, with Special Reference to Morris Rat Hepatomas. J. Nat. Canc. Inst., **38**:839, 1967.

6. Busch, H., Davis, J. R. and Olle, E. W.: Citrate Accumulation in Slices of Transplantable Tumors of the Rat. Canc. Res., **17**:711, 1957.

7. Campbell, J. A. and Cramer, W.: Some Effects of Alteration of Oxygen Pressure in the Inspired Air Upon Cancer Growth and Body Weight of Rats and Mice. Lancet, **1**:828, 1928.

8. Cori, C. F. and Cori, G. T.: The Carbohydrate Metabolism of Tumors. I. The Free Sugar, Lactic Acid, and Glycogen Content of Malignant Tumors. J. Biol. Chem., **65**:11, 1925.

9. Cori, C. F. and Cori, G. T.: The Rate of Glycolysis of Tumor Tissue in the Living Animal. J. Canc. Res., **11**:190, 1927.

10. Dickens, F. and Greville, G. D.: The Metabolism of Normal and Tumor Tissue. XI. The Measurement of Respiratory Quotient, Respiration, and Glycolysis with the Aid of the Constant-Volume Differential Manometer. Biochem. Journ., **27**:1479, 1933.

11. Djerassi, I., Rominger, C. J., Kim, J. S., Turchi, J., Suvansri, U. and Hughes, D.: Phase I Study of High Doses of Methotrexate with Citrovorum Factor in Patients with Lung Cancer. Cancer, **30**:22, 1972.

12. Eden, M., Haines, B. and Kahler, H. The pH of Rat Tumors Measured *In Vivo*. J. Nat. Canc. Inst., **16**:541, 1955.

13. Goldin, A., Greenspan, E. M., Venditti, J. M. and Schoenbach, E. B. Studies on the Biological Interrelationships of Folic Acid, Citrovorum Factor, and the Antimetabolite Aminopterin. J. Nat. Canc. Inst., **12**:987, 1952.

14. Goldin, A., Serpick, A. A. and Mantel, N. Experimental Screening Procedures and Clinical Predictability Value. Canc. Chemother. Rep., **50**:173, 1966.

15. Gullino, P. M., Clark, S. H. and Grantham, F. H.: The Interstitial Fluid of Solid Tumors. Canc. Res., **24**:780, 1964.

16. Gullino, P., Grantham, F. H., Smith, S. H. and Haggerty, A. C.: Modifications of the Acid-Base Status of the Internal Milieu of Tumors. J. Nat. Canc. Inst., **34**:857, 1965.

17. Kahler, H. and Robertson, W. B.: Hydrogen Ion Concentration of Normal Liver and Hepatic Tumors. J. Nat. Canc. Inst., **3**:495, 1943.

18. Kessel, D., Hall, T. C. and Roberts, D. Modes of Uptake of Methotrexate by Normal and Leukemic Human Leukocytes *In Vitro* and Their Relation to Drug Responses. Canc. Res., **28**:564, 1968.

19. Laird, A. K.: Dynamics of Tumor Growth. Brit. J. Canc., **18**: 490, 1964.

20. Levitt, M., Mosher, M. B., DeConti, R. C., Farber, L. R., Marsh, J. C., Mitchel, M. S., Papac, R. J., Thomas, E. D. and Bertino, J. R.: High Dose Methotrexate vs. Methotrexate-Leucovorin in Epidermoid Carcinomas of the Head and Neck. Proc. Am. Assoc. Canc. Res., **13**:80, 1972.

21. Mead, J. A. R., Venditti, J. M., Schrecker, A. W., Goldin, A. and Keresztesy, J. C.: The Effect of Reduced Derivatives of Folic Acid on Toxicity and Antileukemic Effect of Methotrexate in Mice. Biochem. Pharmacol., **12**:371, 1963.

22. McKee, R. W., Lomberg-Holm, K. and Jehl, J. A. Substrate Utilization by Ehrlich Mouse Ascites Carcinoma Cells. Canc. Res., **13**:537, 1953.

23. Meyer, J. A.: Growth-Rate Analysis of Experimental Tumors: A Systematic Method. Arch. Surg., **99**:655, 1969.

24. Meyer, J. A.: Growth Rate Versus Prognosis in Resected Primary Bronchogenic Carcinomas. Cancer, **31**:1468, 1973.

25. Millet, H.: Measurements of the pH of Normal, Fetal, and Neoplastic Tissues by Means of the Glass Electrode. J. Biol. Chem., **78**:281, 1928.

26. Potter, V. R. and Busch, H.: Citric Acid Content of Normal and Tumor Tissues *In Vivo* Following Injection of Fluoroacetate. Canc. Res., **10**:353, 1950.

27. Potter, V. R. and Siekewitz, P.: Pathways of Phosphate Metabolism. *In* A Symposium on Phosphorus Metabolism. Vol. 2. W. D. McElroy, B. Glass, Editors. Baltimore, Johns Hopkins Press, 665, 1952.

28. Racker, E.: Carbohydrate Metabolism in Ascites Tumor Cells. Ann. N. Y. Acad. Sci., **63**:1017, 1956.

29. Schwartz, M.: A Biomathematical Approach to Clinical Tumor Growth. Cancer, **14**:1272, 1961.

30. Sundstroem, E. and Giragossintz, G.: A Demonstration of the Curability of Malignancy in Rats by a Low Pressure Environment. Proc. Soc. Exp. Biol. Med., **27**:511, 1930.

31. Voegtlin, C., Fitch, R. H., Kahler, H., Johnson, J. M. and Thompson, J. W.: The Influence of Parenteral Administration of Certain Sugars on the pH of Malignant Tumors. Nat. Inst. Health Bull., **164**:1, 1935.

32. Warburg, O.: Metabolism of Tumors (Transl. by F. Dickens). New York, R. R. Smith Inc., 1931.

33. Warburg, O., Posener, K. and Negelein, E.: Uber den Stoffwechsel der Karzinomzelle. Biochem. Zeitschr., **152**:309, 1924.

34. Weinhouse, S.: Studies on the Fate of Isotopically Labeled Metabolites in the Oxidative Metabolism of Tumors. Canc. Res., **11**:571, 1954.

35. Zubrod, C. G.: The Basis for Progress in Chemotherapy. Cancer, **30**:1474, 1972.

Surgical Treatment of Gastric Malignancies:

A Twenty-year Series Comprising Mainly Far Advanced and High-seated Tumors

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MOST GENERAL SURGEONS feel qualified to remove small cancers in the distal part of the stomach, and very little progress has been made in this field since William J. Mayo[9] published his series operated upon from 1897 to 1910.

During the past 3 decades advances have taken place in the treatment of patients with extensive and high seated tumors, patients who are often transferred after undue delay to departments having special experience in this field.

Thus, many of these departments receive a very depressing group of patients, which may cause a defeatist attitude. Goldsmith and Ghosh[5] have recently concluded, "If we are going to do anything to improve survival in gastric cancer, the disease must be diagnosed prior to gastric symptoms."

It must be admitted that more effort should be made to diagnose the very early cancers in certain high-risk groups, as has been done on a large scale in Japan, where the disease is more common than in most other countries.[11]

Meanwhile, we have an obligation to try to help the patients we admit, although their disease is far advanced. This paper presents a selected group of advanced cases seen over a twenty-year period.

Material

For this analysis we have chosen a period of twenty years: September 1, 1949 to August 31, 1969. During this period 776 patients with gastric cancer (g.c.) were admitted to the surgical department of the Finsen Institute, Copenhagen.

The patients were referred to us from many parts of Denmark, mainly because of the extent of the tumor or its high situation in the stomach. Most of the patients had previously been admitted to other hospitals. Some of them had already had exploratory operations. Others had been referred by their own doctors after having been rejected by other surgical departments as being inoperable. The material includes relatively few patients with tumors in the distal part of the stomach, as these patients are, in general, treated by surgeons doing a wide range of surgical procedures.

During the whole period the series was changing in a prognostically unfavorable way:

In the second ten-year period. 1) The mean age of the patients had risen from 59.8 years to 64.8. 2) The relative frequency of women, who have a less favorable prognosis than men, had increased, the sex ratio men/women having decreased from 2.6 to 2.0. 3) There were even fewer tumors in the distal stomach, and a larger number of extensive tumors that required total gastrectomy. 4) Histologically there were more far advanced anaplastic tumors with penetration of the gastric wall and metastases to the lymph nodes with breach of the lymph node capsules.

Thus, nearly all our patients are considered inoperable by many surgeons.

General Principles

1. As many patients in a very poor condition can be restored by proper preoperative treatment, we never reject a patient with g.c., even though the patient is

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TABLE 1. *Operability*

Period: September 1, 1949—August 31, 1969	Number	Per cent
Not operated upon	117	15.1
Exploration or G-E anatomosis	334	43.0
Tumor removed	325	41.9
Total	776	100

regarded as inoperable by other surgical departments. In some of these patients it has been possible to perform a radical operation, and some have survived more than 5 years.

2. Since it is often impossible to decide beforehand whether a tumor is operable, every patient who could be made fit for operation should have an exploratory operation.

3. Removal of the tumor being the best kind of palliation, every tumor should be removed, if technically possible. Unlike most other surgeons, we also use total gastrectomy for palliation, unless there is diffuse carcinosis with ascites or multiple metastases to the liver.

In cases where the tumor could not be removed, gastroenterostomy was used for distal tumors and luminal tubulation for tumors of the cardia. However, these procedures give only brief palliation.

Operability

As will be seen from Table 1, about 15% of the patients were not operated on, either because they died shortly after admission, refused operation, or could not be rendered fit for operation by preoperative treatment.

Eighty-five per cent of the patients were operated on, but 43% had only exploration or some kind of short-circuit operation.

In about 42% of the patients the tumor could be removed, but the operation could be classified as radical in only 38% of these patients.

Despite more unfavorable cases during the second 10-year period, it was possible during that period to remove a higher percentage of tumors by a relative larger number of total gastrectomies.

Operative Methods

It has been our aim to remove the gastric tumor together with the omentum, the regional lymph nodes, and to resect invaded adjacent organs at a safe distance from the tumor, without being more radical than necessary.

Thus, we have not routinely adhered to a standard technique, but have employed the technique which we have considered most suitable and which appeared to serve the patient best. Apart from the first few years, most of our radical operations have been what is described as "extensive procedures," while the palliative operations generally have been of less extent.

The extent and radicalness of the operation is decided during the operation by the aid of frozen section microscopy, which in our opinion is mandatory in cancer surgery. The lines of resection are always checked microscopically.

According to the site and extent of the tumor, a lower, middle, or upper resection has been carried out, and in the most extensive tumors, where no part of the stomach could be spared, total gastrectomy was performed.

The upper resections and the total gastrectomies are carried out through combined abdomino-thoracic incisions and most often with removal of the spleen and the distal two-thirds of the pancreas. If necessary, also the left adrenal, the transverse colon or the left lobe of the liver have been removed. In upper resections a rim of the adjacent diaphragm is usually resected together with the tumor.

In all partial resections the entire lesser curvature is removed for the following reasons: 1) the lesser curvature is the most frequent site of carcinomas and must be suspected as a precancerous region, 2) if the tumor is situated on the lesser curvature, it most often spreads along the curvature. 3) In these cases also the lymphatic metastases spread along the lesser curvature, and they are removed more easily and radically by removing the whole curvature. 4) This procedure facilitates the establishment of the anastomoses, since a new lesser curvatuve is created.

As radical operations (attempted cure) we have designated those in which the resection of the esophagus or stomach has been performed at a distance of at least 5 cm. from the gross limits of the tumor, in the duodenum 3 cm., and where no grossly visible tumor tissue has been left. The others are classified as palliative.

The frequency of the various operative procedures is shown in Table 2.

Because of the high percentage of very advanced cases, total gastrectomy was the most frequent procedure. After a short period during which we used the now obsolete

TABLE 2. *Operative Procedures*

Operative Method Period: September 1, 1949—August 31, 1969	Number	Per cent
Total gastrectomy	131	40.3
Upper gastric resection	105	32.3
Middle gastric resection	7	2.2
Lower gastric resection	82	25.2
Total	325	100

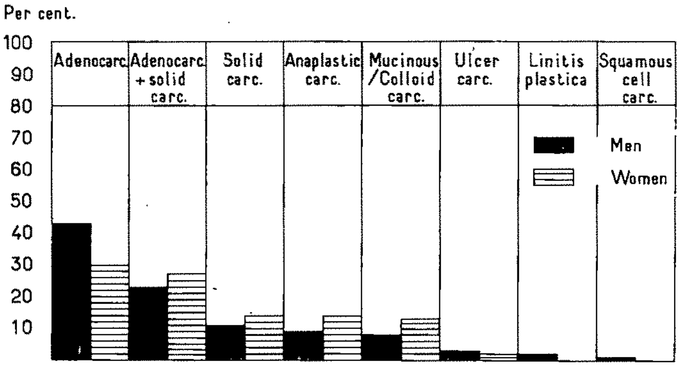

FIG. 1. Relative frequency of various types of carcinoma in men and women.

end-to-side anastomosis, we changed to the Roux-Herzen end-to-end anastomosis in 1949, on the recommendation of Allison and Borrie.[1] Since 1957, however, we have preferably used interposition of the jejunum, as described by Longmire and Beal[8] or if this method is inapplicable for technical reasons, interposition of the transverse colon by the method of State, Barclay, and Kelly,[10] but with the colon placed in an isoperistaltic direction as described by Zacho and Skielboe.[16]

The procedure next in frequency has been upper resection, because of the great number of high seated tumors. The reconstruction has usually been by esophagogastrostomy, or if the gastric stump has been too short, sometimes by proximal intestinal interposition by Zacho's method.[13]

Middle resection[12] has been used in only few cases, mostly as a palliative measure in old patients.

Lower resection, which is by far the most common operation in unselected series, was performed in only 25%, the distal tumors being usually handled in the local hospitals.

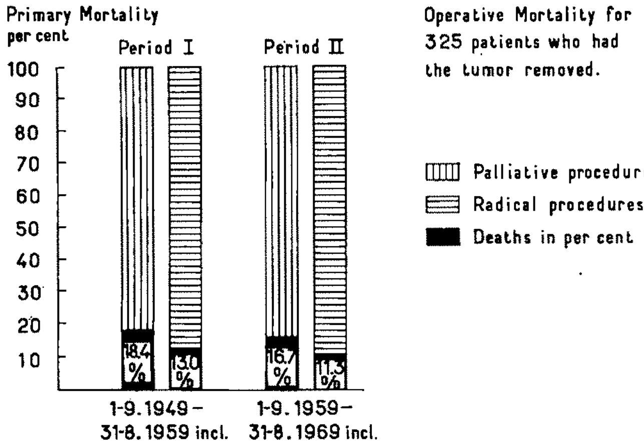

FIG. 2. Operative mortality.

TABLE 3. *Operative Mortality for Radical Procedures During the Second Ten-year Period*

Period: September 1, 1959—August 31, 1969

Procedure	Radical Number	Mortality Number	Mortality Per cent
Total Gastrectomy	32	4	13
Upper Resection	23	4	17
Lower Resection	15	0	0
Middle Resection	1	0	0
Total	71	8	11

Pathology

Of the 325 tumors removed, 313 were carcinomas and 12 sarcomas. All the tumors were invasive. No tumor was classified as cancer on cytologic criteria alone (Fig. 1).

Most of the tumors were situated in the upper or middle part of the stomach. Tumors in the lower part were relatively rare in this series, especially during the latter period. Many of the tumors apparently originating from the upper or lower part of the stomach had extended to nearly the whole stomach.

The predominant proportion of the tumors were adenocarcinomas, which are most common in men. Except for linitis plastica of which there were only a few cases, the most malignant types, such as solid carcinoma, anaplastic, and colloid carcinomas, were relatively more frequent in women than in men.

It is well-known from the works of Broders[2] that the less differentiated the tumor the worse the prognosis, the anaplastic tumors (grade 4) having the worst prog-

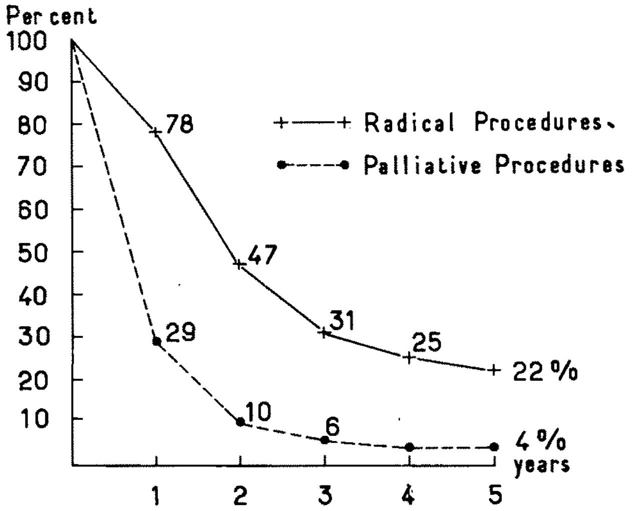

FIG. 3. Survival curves for patients who survived total gastrectomy.

nosis. Dukes[3] has shown the significance of penetration, which has been used by Lewin[7] for a more detailed classification.

In our clinic[15] we have demonstrated that metastases to the lymph nodes do not essentially aggravate the prognosis, provided that the capsules of the lymph nodes are intact and the involved lymph nodes are removed. But if the metastatic tumor cells have penetrated the node capsules and have spread to the surrounding tissues the chance of survival is extremely small.

In 86% of the patients in whom the tumor was removed, the tumor had penetrated the gastric wall, spread to the surrounding tissues, and metastasized to the lymph nodes or other organs.

Operative Mortality

In recent years there has been a tendency to limit the term: operative mortality to the percentage of patients who die within 30 days as a direct consequence of the operation.

Today, however, it is possible to keep patients alive for more than 30 days after postoperative complications from which they may succumb later.

Therefore, we take operative mortality to mean the percentage of operated patients who die during their stay in hospital, regardless of whether their death is considered to be caused by the operation and regardless of the duration of their stay in hospital. It includes also patients who were transferred, because of postoperative complications, to other departments for special treatment and who died there.

Fig. 2 presents the mortality for the two 10-year periods. As will be seen, the mortality rate has decreased very little from the first to the second period.

Although the palliative operations are generally of a lesser extent than the radical operations, they carry a higher operative mortality, as these patients die of their advanced cancer rather than of the operation.

Table 3 gives the values for radical operations alone for the second 10-year period.

The mortality changes a great deal for every 5-year period, apparently not only because of changes in the gravity of cases, but also because of changes in the quality of the staff. The cases recorded in this paper were operated on by about a dozen different surgeons among whom only one has been permanent through the whole period. In our opinion operations of this kind should be performed only by surgeons who have special training and experience in this field.

Upper resections carry a higher mortality than total gastrectomy, because the tumor often extends higher in the esophagus, so that the anastomosis has to be established at a higher level than in total gastrectomy.

When assessing the mortality rate for the 2 periods it must be borne in mind that during the second period the mean age of the patients in whom the tumor was removed was about 5 years higher than in the first period. Moreover, the tumors of the second period were farther advanced.

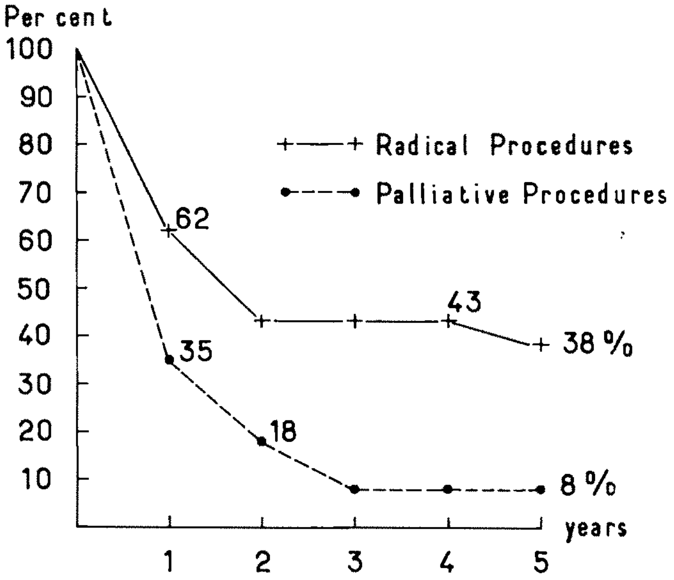

FIG. 4. Survival curves for patients who survived upper gastric resection.

Late Results

All patients who have survived removal of the tumor before September 1, 1964 have been followed for at least 5 years or until their death.

In assessing the survival rate, it must be borne in mind that in these age groups there is an appreciable mortality in the general population from other causes, for which no correction has been made.

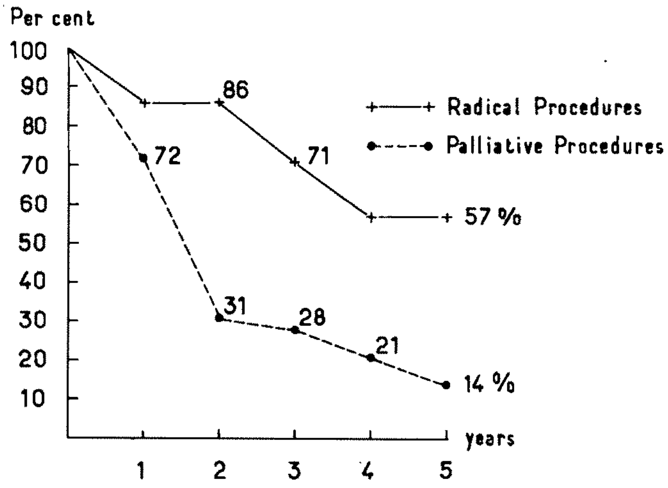

FIG. 5. Survival curves for patients who survived lower resection.

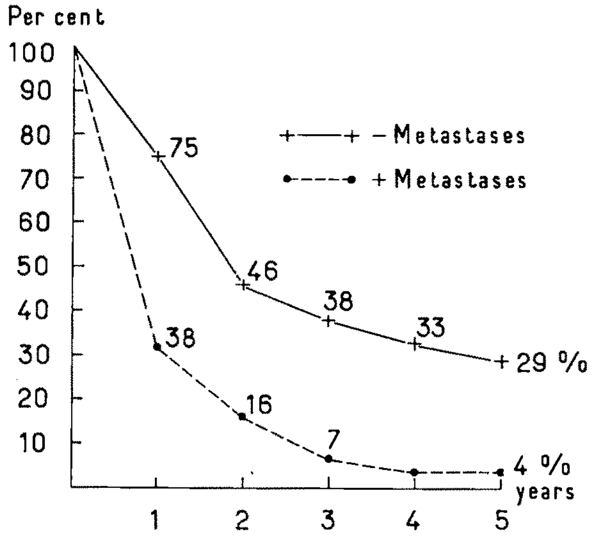

FIG. 6. Survival curves for patients who survived total gastrectomy, including those who had palliative operations.

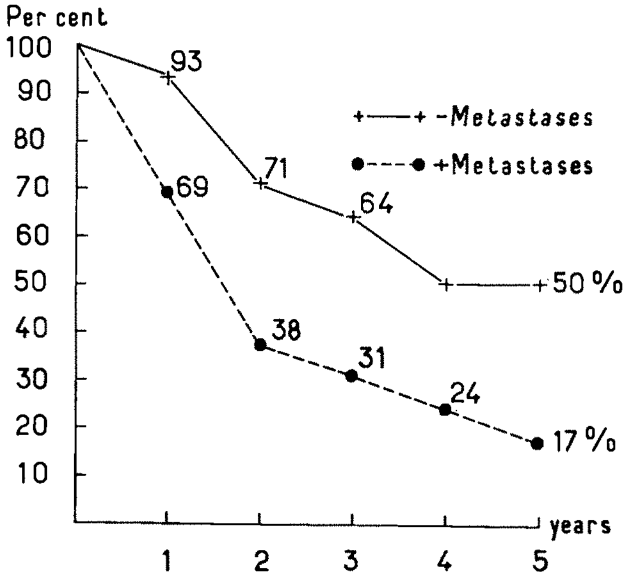

FIG. 8. Survival curves for patients who survived lower resection, including those who had palliative operations.

Survival in Relation to Operative Procedure

We have calculated the survival for each operative procedure separately, except for the few middle resections which are included in Figs. 9 and 10.

As already mentioned, we distinguished between radical (attempted cure) and palliative procedures. This distinction is based on an evaluation of the extent of the procedure practicable under the given circumstances and the extent of the tumor, determined by the aid of microscopy of frozen sections during the operation.

If the distinction between radical and palliative operations had been correct, all patients who had been submitted to a radical operation ought to be alive at the end of 5 years except those who died from other causes, and all or nearly all patients who have had a palliative operation ought to have died.

As may be seen from Figs. 3–5, results did not fall into place this neatly. In particular, the radicality of the "radical" procedures has been overestimated. At the time of operation it may be impossible to say for certain whether the liver contains metastases, or whether the

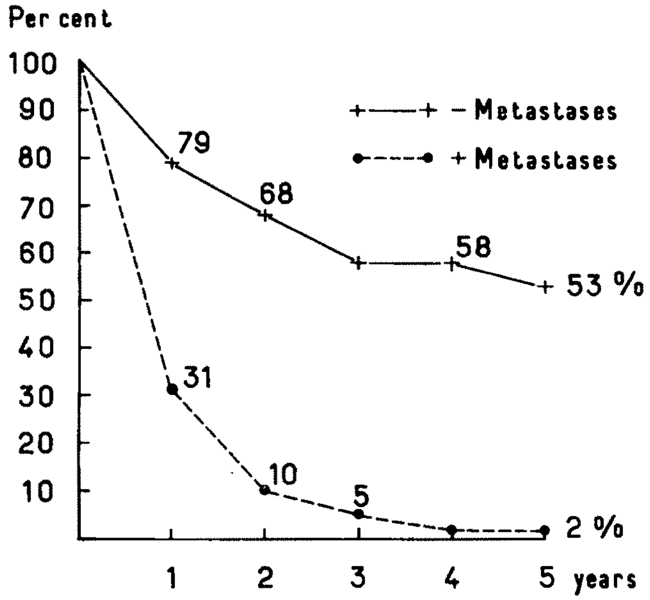

FIG. 7. Survival curves for patients who survived upper resection, including those who had palliative operations.

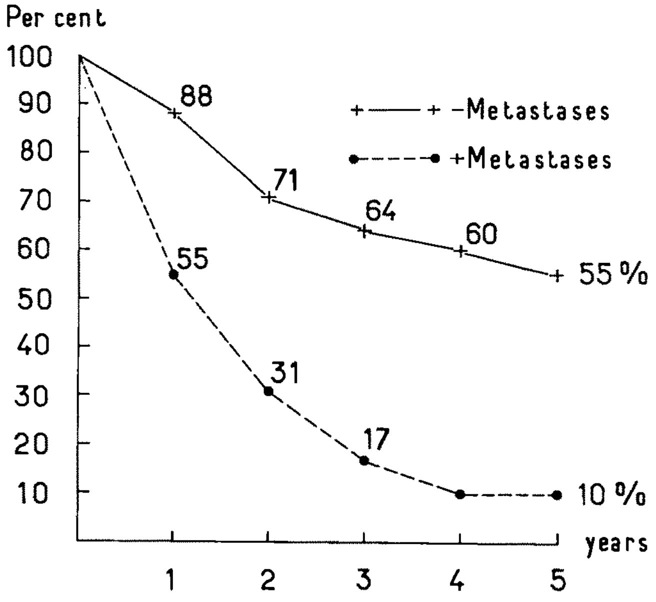

FIG. 9. Survival curves for all patients who survived removal of the tumor by radical operation.

lymph nodes contain tumor cells, even on the basis of microscopy. Thus, an operation which in fact is only palliative may have been classified as radical.

On the other hand, very extensive tumors, that could be resected only at a very short distance, may have been removed curatively, because the invasion into the surrounding tissues has been very limited.

Furthermore, the immunological resistance of the patient must be taken into consideration. Very big exophytic tumors which protrude into the lumen of the stomach because the defense system of the body prevents them from infiltrating the surroundings, are much more benign than the flat infiltrating cancers which rapidly infiltrate the surroundings, sometimes without producing demonstrable lymph-node metastases.

As expected, the total gastrectomies, performed for extensive tumors in the corpus or for extensive tumors originating from the upper or lower part of the stomach, are followed by the lowest survival rate.

Lower resection, in most surgical departments the most frequent procedure and in many departments the only one, gives the best prognosis.

Upper resection performed for tumors at the cardia and in the upper part of the body of the stomach, lies in between.

Survival in Relation to Histological Type of Tumor

Of the patients who survived removal of the tumor before September 1, 1964 only 7 had sarcomas, 2 of them survived more than 5 years, both after a radical middle resection. Of the remaining 5 patients, 2 had "radical" and 3 palliative operations, but none survived more than 4 years.

Table 4 demonstrates the survival rates for the various types of carcinoma. Ulcer carcinomas, which number only 5, seem to have the best prognosis, followed by adenocarcinomas which make up the largest group. The table shows the severe malignancy of the colloid tumors; no patient of this group survived 5 years. In an earlier study[15] we had no 5-year survivors with anaplastic carcinomas, but since then we have had 3.

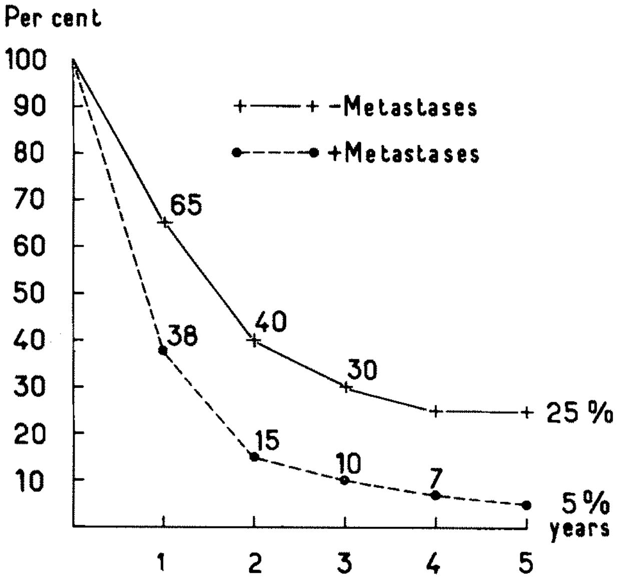

FIG. 10. Survival curves for all patients who survived removal of the tumor by palliative operation.

Survival in Relation to Lymph-Node Metastases

Jamieson and Dobson[6] felt that when the gastric cancer had metastasized to the lymph nodes no cure was possible. Unfortunately, this opinion has been shared by many surgeons since then. This has been all the more tragic as no doubt many patients with enlarged lymph nodes have been closed as inoperable without having had any metastases at all.

The values for frequency of metastases to the lymph nodes are minimum values, since in several of the numerous palliative operations the dissection of the lymph nodes has been incomplete. Furthermore, the frequency of

TABLE 4. *Survival in Relation to Pathology in 183 Patients who Survived Radical or Palliative Removal of Gastric Carcinoma from September 1, 1949 to August 31, 1964. (One of the Tumors from the Upper Resections was Excluded, its Histologic Type being Uncertain.)*

Radicality	Operation	Metastases to lymph nodes		No metastases to lymph nodes	Total	Per cent of total number of tumors	Survival more than 5 years	Survival in per cent of each group of tumors
Radical procedures 67 Palliative procedures 116	Total gastrectomy 77 Upper resection 60 Lower resection 43 Segmental resection 3	No breach of capsule	Breach of capsule					
Adenocarcinoma		15	23	33	71	39	18	25
Adenocarcinoma and solid carcinoma		7	22	15	44	24	8	18
Solid carcinoma		4	13	5	22	12	3	14
Mucoid or colloid carcinoma		3	8	6	17	9	0	—
Anaplastic carcinoma		4	9	7	20	11	3	15
Linitis plastica		1	0	2	3	2	0	—
Squamous-cell carcinoma		1	0	0	1	0	0	—
Ulcer carcinoma		0	2	3	5	3	2	40
	Total	35	77	71	183	100	34	19

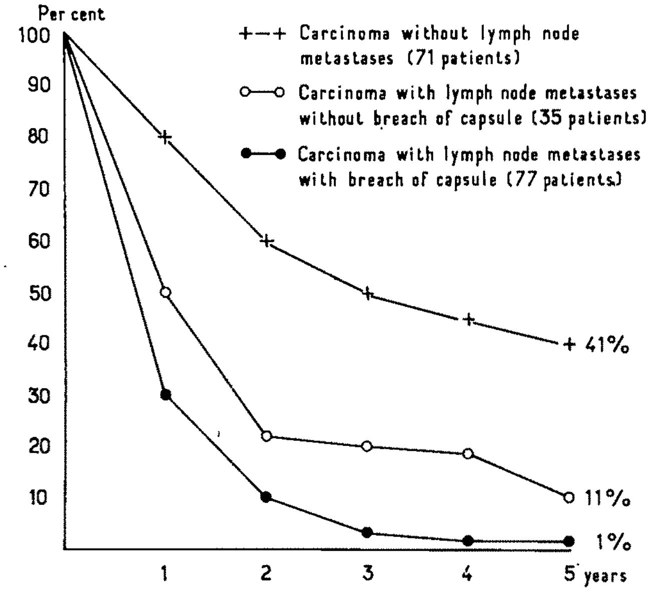

FIG. 11. Survival curves demonstrating the prognostic significance of lymph-node metastases with and without penetration (breach) of the node capsules. 183 patients who had the tumor removed, including palliative operations.

finding metastases depends on the varying interest and energy of the pathologist.

The prognostic role of lymph-node metastases is shown in Figs. 6–11. The prognosis is best after the lower resections. On the other hand, patients who have had upper resections are almost safe after 3 years, while the survival curve after lower resection goes on declining.

Although the presence of metastases to the lymph nodes aggravates the prognosis, it has been demonstrated by Zacho, Fischermann and Sørensen[15] that the crucial point is whether the capsules of the lymph nodes have been penetrated by tumor cells. After exclusion of the most malignant anaplastic tumors and those in which the capsules of the lymph nodes have been penetrated by tumor tissue, the prognosis is approximately the same in cases with and without metastases to the lymph nodes, provided, of course, that the involved lymph nodes are removed. Once the capsules of the lymph nodes have been penetrated by the tumor tissue, the chances of cure by surgery alone are minimal (Fig. 11).

Classification

In our opinion, every classification of g.c. based only on the surgeons' macroscopic assessment at the time of operation is of little value, because it is subject to individual variations.

We have tried to classify our carcinomas on a histological basis only. As already mentioned, this is subject to individual variations too, but only in one direction: under-estimation, because grave prognostic factors may have been overlooked.

Table 5 demonstrates that, if the carcinoma is confined to the stomach within the serosa, the survival rate is high in all grades of differentiation except grade 4 (anaplastic). Penetration beyond the serosa aggravates the prognosis essentially just as do metastases to the lymph nodes. But there is still a reasonable chance of cure if a "radical" procedure can be performed. If the anaplastic tumors (grade 4) and lymph-node metastases with breach of the node capsule are included, the chance of survival is small, even when the operations seem to have been technically "radical."

Late Postoperative Condition

Postoperative trouble, such as pain, dysphagia, vomiting etc. may be caused by recurrence, especially if occurring after a free interval.

Therefore, the final assessment of the postoperative condition after the various procedures is best carried out after 5 years, when the possibility of recurrence is small.

Patients who have had lower resections are, on the whole, free of symptoms.

Patients who have had upper resections are the group having most trouble. About one-half are, on the whole, free of symptoms. About one-third complain of epigastric pain, if they eat too much at a time, or they have regurgitation upon stooping or lying down. In some of these cases, it has been found necessary to carry out a supplementary pyloroplasty which is not performed routinely.

TABLE 5. *Survival Rates for Various Stages of Carcinomas Removed by "Radical" Procedures*

Classification	Differentiation (Broders)		Lymph-node Metastases					
	All grades excluding anaplastic	Anaplastic	With breach of capsule	Without breach of capsule	Penetration beyond the serosa	Total number	5-year Survivors	
Stage							Number	Per cent
I	17					17	13	76
II	16				16	16	7	44
III	5			5		5	2	40
IV	20	9	20	3	19	29	2	7
Total	58	9	20	8	35	67	24	34

It is often mentioned[5] that total gastrectomy frequently renders the patient nutritionally disabled. We had the same experience with the old method of end-to-side esophago-jejunostomy, but since we changed to the interposition methods we have had no serious nutritional problems with these patients.[4,14] Especially the patients who have interposition of the jejunum by the Longmire and Beal method recover more quickly than patients treated by other methods. They are able to lead a normal life and are capable of working. This method is, in our opinion, one of the greatest advances in the treatment of extensive gastric cancers.

Summary

A survey is given of the results of treating 776 patients with gastric cancer from a 20-year period, the majority with advanced and high seated tumors.

Despite increasing age and increasing frequency of far advanced cases, it was possible during the second 10-year period to remove more tumors at a slightly lower mortality.

Of the patients in whom a technically "radical" procedure was possible and who survived the operation, 22% having total gastrectomy, 38% having upper resection, and 57% having lower resection were alive at 5 years.

Of the survivors after "radical" procedures of all kinds, 55% without and 10% with metastases to the lymph nodes, were alive at 5 years. After palliative procedures the corresponding values were 25% and 5%.

References

1. Allison, P. R. and Borrie, J.: The Treatment of Malignant Obstruction of the Cardia. Brit. J. Surg., **37**:1, 1949–1950.
2. Broders, A. C.: Squamous-Cell Epithelioma of the Lip. JAMA, **74**:656, 1920.
3. Dukes, C. E.: The Classification of Cancer of the Rectum. J. Pathol., **55**:I, 323, 1932.
4. Fischermann, K., Harly, S., Worning, H. and Zacho, A.: Pancreatic Function and the Absorption of Fat, Iron, Vitamin B_{12} and Calcium after Total Gastrectomy for Gastric Cancer. Gut, **8**:260, 1967.
5. Goldsmith, H. S. and Ghosh, B. C.: Carcinoma of the Stomach. Am. J. Surg., **120**:317, 1970.
6. Jamieson, J. K. and Dobson, J. F.: The Lymphatic System of the Stomach. Lancet, **85**:1061, 1907.
7. Lewin, E.: Gastric Cancer. Acta Chir. Scand. suppl. 262, 1960.
8. Longmire, W. P. and Beal, J. M.: Construction of a Substitute Gastric Reservoir following Total Gastrectomy. Ann. Surg., **135**:637, 1952.
9. Mayo, W. J.: Radical Operation for Cancer of the Pyloric End of the Stomach. JAMA, **20**:1608, 1910.
10. State, D., Barclay, T. and Kelly, W. D.: Total Gastrectomy with Utilization of a Segment of Transverse Colon to Replace the Excised Stomach. Ann. Surg., **134**:1035, 1951.
11. Takada, H.: Characteristics of X-Ray Diagnosis of Early Gastric Cancer in Mass Examination of the Stomach. In Gann Monograph on Cancer Research No. 11. Baltimore, London, Tokyo, University Park Press. 131, 1972.
12. Zacho, A.: A Method of Gastric Resection for Peptic Ulcer of the Stomach. Acta Chir. Scand., **110**:187, 1955.
13. Zacho, A.: Antrum-Preserving Operation with Interposition of Jejunum following Resection of Carcinoma in the Upper Part of the Stomach. Danish Med. Bull., **7**:132, 1960.
14. Zacho, A. and Fischermann, K.: The Results of Surgical Treatment of Cancer of the Stomach. Surg., Gynecol. Obstet., **123**:73, 1966.
15. Zacho, A., Fischermann, K. and Sørensen, B. L.: Prognostic Role of Breach of Lymph Node Capsule in Nodal Metastases from Gastric Carcinoma. Acta Chir. Scand., **125**: 365, 1963.
16. Zacho, A. and Skielboe, B.: Transverse Colon as a Substitute for the Stomach following Total Gastrectomy for Cancer. Danish Med. Bull., **4**:205, 1957.

Skin Knife-Deep Knife:

The Ritual and Practice of Skin Incisions

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THE PRACTICE IN SURGERY has been to discard the knife blade following its use on the skin, even if it is not dull and is the correct size to continue deeper. There has been much research on skin bacterial flora and skin preparation, mostly decades ago, which supported this custom. The following questions must be considered: the nature of normal skin flora, its possible sterilization in surgical preparation, and the presence of pathogenic organisms.

The old literature that supported this outdated custom include studies by Welch[12,13] who isolated microorganisms from sweat and previously surgically prepared skin, and cultured skin sutures passed through the prepared skin. The only bacteria he found was the benign "white staphylococcus." Harrington[5] cultured sweat and found it sterile. Tinker and Sutton[11] cultured skin scrapings of unprepared skin. Most of these were sterile. Arnold[1,2] demonstrated that sweat is a good culture medium but that the intact stratum corneum tends to sterilize itself, and this is probably related to pH. Arnold and Bart[1] presented evidence that keratin may play a role in removal of bacteria. Microorganisms placed on the skin disappeared rapidly and not as a result of drying. Price[9] believed that the bacterial flora were on the surface and presented evidence that sweat was sterile and that infection originating in sebaceous glands was rare. He demonstrated that plucked hairs from well-washed skin were sterile. The degree of hariness had almost no relation to the number of cultured bacteria and the microscopic examination of the deeper layers of the skin did not reveal any bacteria. Ricketts, Squire and Topley[10] demonstrated the self-sterilizing power of skin by demonstrating the elimination of staphylococcus aureus from the skin by the use of occlusive dressings.

However, Evans[4] correlated positive skin cultures with the number of sebaceous glands in various locations of the body and concluded that these glands were the major source of skin bacteria. Lovell[6] found skin secretions to be sterile, but by culturing the skin itself, found staphylococcus in some hair follicles.

Materials and Methods

Thirty-one patients operated on consecutively by the author or with his assistance were studied (Table 1). All the operations were through fresh skin incisions and many different types of general surgical operations were performed. The preparation of the skin was with a preoperative night skin shaving and Betadine soap wash, and in the operating room a 5-minute Betadine scrub followed by painting with Betadine antiseptic solution.

Following completion of the skin incision, the knife blade was sterily placed into an upright glass vial containing 10 ml of thioglycolate broth. This was cultured for aerobic and anaerobic organisms. The incision was then irrigated with fresh, sterile saline at room temperature, taken from the irrigation basin. Approximately 2 ml per linear centimeter was used, and all the irrigation fluid plus active swabbing of the skin edges was cultured, both qualitatively and quantitatively. The procedure was repeated at the conclusion of the operation prior to skin closure. The irrigation solutions were cultured both on blood agar plates and in thioglycolate broth.

Staphylococcus epidermidis (albus) in final dilutions of one thousand organisms per milliliter served as con-

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trols. The organisms were grown in normal saline, 1/10 milliliter Betadine in saline solution, thioglycolate broth, and in thioglycolate broth with 1/10 milliliter of Betadine. After 48 hours the organisms were quantitated.

In a second study, 73 patients had their skin cultured as they arrived in the operating room prior to skin preparation. As in the first group of patients, their skin was shaved and washed with Betadine soap the night prior to surgery.

Results

Of the 31 scalpel blade cultures, one culture contained the non-pathogenic staphylococcus epidermidis (Table 1). Of the 31 incision irrigations and swabbings performed at the beginning of surgery, 3 cultures were positive for normally non-pathogenic organisms. Four positive cultures were obtained prior to skin closure. One contained staphylococcus epidermidis (consistent on all 3 cultures). The other 3 were operations which opened the stomach or esophagus and cultures yielded gamma or alpha hemolytic stretococci.

The control cultures of staphylococcus epidermidis in normal saline remained unchanged in number after 24 hours, while the 1/10 milliliter Betadine in saline solution was without viable organisms after 24 hours. The staphylococcus epidermidis multiplied heavily in the thioglycolate broth, both without and with the Betadine solution.

Of the 78 preoperative patient skin cultures, 33 percent were sterile and 67% had only staphylococcus epidermidis (albus) as flora. It is significant that no pathogenic organisms were found.

Discussion

More recently a number of pertinent and thorough bacteriologic studies were done. In an epidemiological study of staphylococcal infections in the operating room. Wise, Sweeney, Haupt, and Waddell[14] did numerous cultures including air, nasal, rinse water, skin and instruments. Eighty per cent of the wounds yielded positive cultures but of these 71 patients, no infection occurred in 68 of them. Phage typing could not verify the source of the bacteria in the three infected patients. Wound irrigations yielded 17% coagulose positive and 42% coagulose negative staphylococcus epidermidis; a similar per cent was found in their instrument rinse water. They did not state the source of their irrigation fluid and therefore the true incidence of positive wound and skin cultures in their study is questionable.

Pecora[7] cultured full thickness pieces of skin taken from the wound margin at the conclusion of 65 consecutive (clean) major operations. All were sterile except for one culture yielding one *Staphylococcus epidermidis* (albus) colony.

In a well controlled study, Pecora, Landis, and Martin[8] biopsied full thickness skin edges from clean cases at the beginning of surgery, plus skin washings and fascia cultures. All biopsy cultures and microscopic slides revealed no organisms.

Davidson and Smith[3] performed cultures during 1,000

TABLE 1.

Operative Procedure	Knife Blade	Cultures: Initial Irrigation & Swabbing	Cultures: Final Irrigation & Swabbing
1. Cholecystectomy Appendectomy	—	—	—
2. Thyroidectomy	—	—	—
3. Herniorrhaphy—(torn glove during procedure)	Staphylococcus Epidermidis	Few organisms of *Staphylococcus epidermidis*	One colony *Staphylococcus epidermidis*
4. Cholecystectomy	—	—	—
5. Exploratory Laparotomy	—	One colony of diptheroids	—
6. Cholecystectomy	—	—	—
7. Cholecystectomy, Appendectomy	—	—	—
8. Cholecystectomy	—	—	—
9. Colon Polypectomy	—	—	—
10. Exploratory Laparotomy	—	—	—
11. Inguinal Herniorrhaphy	—	—	—
12. Abdominal Wall Lipoma Excision	—	—	—
13. Sympathectomy	—	—	—
14. Cholecystectomy, Appendectomy	—	—	—
15. Inguinal Herniorrhaphy	—	—	—
16. Gastrostomy	—	—	300 alpha hemolytic streptococci
17. Radical Mastectomy	—	—	—
18. Thyroidectomy	—	—	—
19. Inguinal Herniorrhaphy	—	—	—
20. Inguinal Herniorrhaphy	—	—	—
21. Hiatial Herniorrhaphy (Thoracic)	—	—	—
22. Sigmoid Polypectomy	—	—	400 gamma hemolytic streptococci
23. Left Colectomy	—	—	—
24. Cholecystectomy	—	—	—
25. Colon Resection	—	—	—
26. Illeo-Colostomy	—	2400 *Staphylococcus epidermidis*/ml	—
27. Breast Biopsy	—	—	—
28. Hiatial Herniorrhaphy (Thoracic)	—	—	—
29. Thyroglossal Duct Cyst Excision	—	—	—
30. Cholecystectomy	—	—	—
31. Esophago-Gastrostomy	—	—	1800 alpha hemolytic streptococci/ml

surgical procedures. These included skin before and after preparation, nasal, bandages, subcutaneous tissue, suture line at the end of the operation, air, masks, and hands of the operating team. They concluded that the wound sepsis associated with *Staphylococcus aureus* seemed to arise most frequently as a result of ward gross infection.

In 31 consecutive general surgical and thoracic operations, the author has shown no pathogenic organisms were found on the scalpel blades or skin following routine preparation in the operating room. Only one scalpel blade had a positive culture and this was *Staphylococcus epidermidis*. This patient had positive irrigation and swabbing cultures following the skin incision and prior to its closure. The separate deep knife, even though it was used, did not protect the wound. Following operations which gained entry to the lumen of the esophagus or stomach, alpha and gamma hemolytic streptococci were cultured. These are found in saliva, and a deep knife is of no help.

All the patients were followed postoperatively and only one wound infection occurred. This patient had a cholecystectomy and incidental appendectomy, with the author as assistant. During the appendectomy a small fecalith fell into the abdomen and was removed. The drain exited through the wound and on the seventh postoperative day, an *E. coli* wound abscess was drained. The third culture in the study, in addition to the blade and the initial incision cultures, was sterile. It is felt that the bacteria migrated into the wound after surgery along the drain either from within the abdominal cavity or from without.

The cultures were not affected by any residual Betadine on the skin knife or wound during irrigations. This was demonstrated by the lack of bacterial inhibition of the control thioglycolate cultures with Betadine solution while the Betadine was bacteriocidal in saline solution. The sulphydryl groups in the thioglycolate culture medium inactivates the Betadine (reduces the molecular to the ionic form and therefore inactive form).[8]

There were no pathogenic bacteria found on the skin of 73 patients who were cultured prior to the operating room skin preparation. They had the routine shaving and Betadine soap skin washing the previous night.

The author's studies of the skin incision, scalpel blade plus wound irrigation and swabbing, evaluated with regard to the excellent studies of Pecora,[7] Pecora, Landis, and Martin,[8] and Davidson and Smith[3] strongly militates against continuing this useless procedure. The blade should be changed, upon the surgeon's request, if it is dull or if a different size is needed.

There is inconsistency in practice because skin edge remains open throughout surgery. Wound towels, which become wet, can transmit bacteria, are removed prior to skin closure and therefore offer no theoretical or practical protection. Plastic skin adhesive drapes do not cover skin edges. Suturing the skin at the termination of surgery causes this needle and suture material to transverse through the surface of the skin into the depth of the subcutaneous tissues innumerable times. The wasteful and inconsistent skin knife–deep knife practice should be terminated in the light of recent studies.

Summary

The practice in surgery has been to discard the sharp scalpel blade following its use on the skin because of the fear that its surface may possibly be contaminated, and therefore would drag pathogenic organisms into the depths of the wound. Thirty-one consecutive surgical patients had the scalpel blades used on the skin cultured, and the skin edges irrigated and swabbed following incision and prior to skin closure. All blades and cultures were consistently sterile except one had all 3 cultures positive for *Staphylococcus epidermidis*.

The necessity for discarding a sharp scalpel blade following its use on the skin should no longer be a mandatory practice imposed upon surgeons.

References

1. Arnold, L. and Bart, A.: The Self-Disinfecting Power of the Skin, Am. J. Hyg., **19**:217, 1934.
2. Arnold, L., Gustafson, C. J., Hull, T. G., Montgomery, B. E. and Singer, C.: The Self-Disinfecting Power of the Skin as a Defense Against Microbic Invasions, Am. J. Hyg., **11**: 345, 1930.
3. Davidson, A. and Smith, G.: Bacteriological Studies in the Operating Theatre in Relation to Postoperative Wound Sepsis, Brit. J. Surg., **56**:705, 1969.
4. Evans, C. A., Smith, W. M., Johnston, E. A. and Gilbett, E. R.: Bacterial Flora of the Normal Human Skin, J. Invest. Dermat., **15**:305, 1950.
5. Harrington, C.: Some Studies in Asepsis, Ann. Surg., **40**:475, 1904.
6. Lovell, B. L.: Skin Bacteria: Their Location With Reference To Skin Sterilization, Surg, Gynec. & Obst., **80**:174, 1945.
7. Pecora, D. V.: Microorganisms on the Skin, Arch. Surg., **80**: 1056, 1960.
8. Pecora, D. V., Landis, R. E., Martin, E.: Location of Cutaneous Microorganisms, Surg., **64**:1114–8, Dec., 1968.
9. Price, P. B.: The Bacteriology of Normal Skin; A New Quantative Test Applied to the Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleansing, J. Infect. Dis., **63**:301, 1938.
10. Ricketts, C. R., Squire, J. R. and Topley, E.: Human Skin Lipids With Particular Reference to the Self-Sterilizing Power of the Skin, Clin. Sc., **10**:89, 1951.
11. Tinker, M. B. and Sutton, H. B.: The Efficiency and Inefficiency of Certain Skin Antiseptics, Ann. Surg., **83**:640, 1925.
12. Welch, W. H.: Conditions Underlying the Infections of Wounds, Am. J. M. Sc., **102**:438, 1891.
13. Welch, W. H.: General Bacteriology of Surgical Infections. *In* System of Surgery. F. S. Dennis, editor. Philadelphia, Lea Bros, & Co., 250, 1895.
14. Wise, R. I., Sweeney, F. J., Haupt, G. J. and Waddell, M. A.: Ann. Surg., **149**:30, 1959.

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(dioctyl sodium sulfosuccinate with casanthranol)

How supplied:

Comfolax-*plus* is supplied in capsules of two-toned green, containing 100 mg. of dioctyl sodium sulfosuccinate and 30 mg. of casanthranol, a gentle stimulant; in trade-size packages of 10 and 60 capsules, and in unit-dose cartons of 1,000 capsules for hospital use.

Dosage:

The recommended adult dose is 1 or 2 capsules at bedtime for 1 or 2 days, then 1 capsule daily as needed. Because of its dosage size, Comfolax-*plus* is not recommended for use by children less than 12 years of age.

Warnings: Do not use Comfolax-*plus* when abdominal pain, nausea or vomiting is present. Frequent or prolonged use of this preparation may result in dependence on laxatives.

4G1

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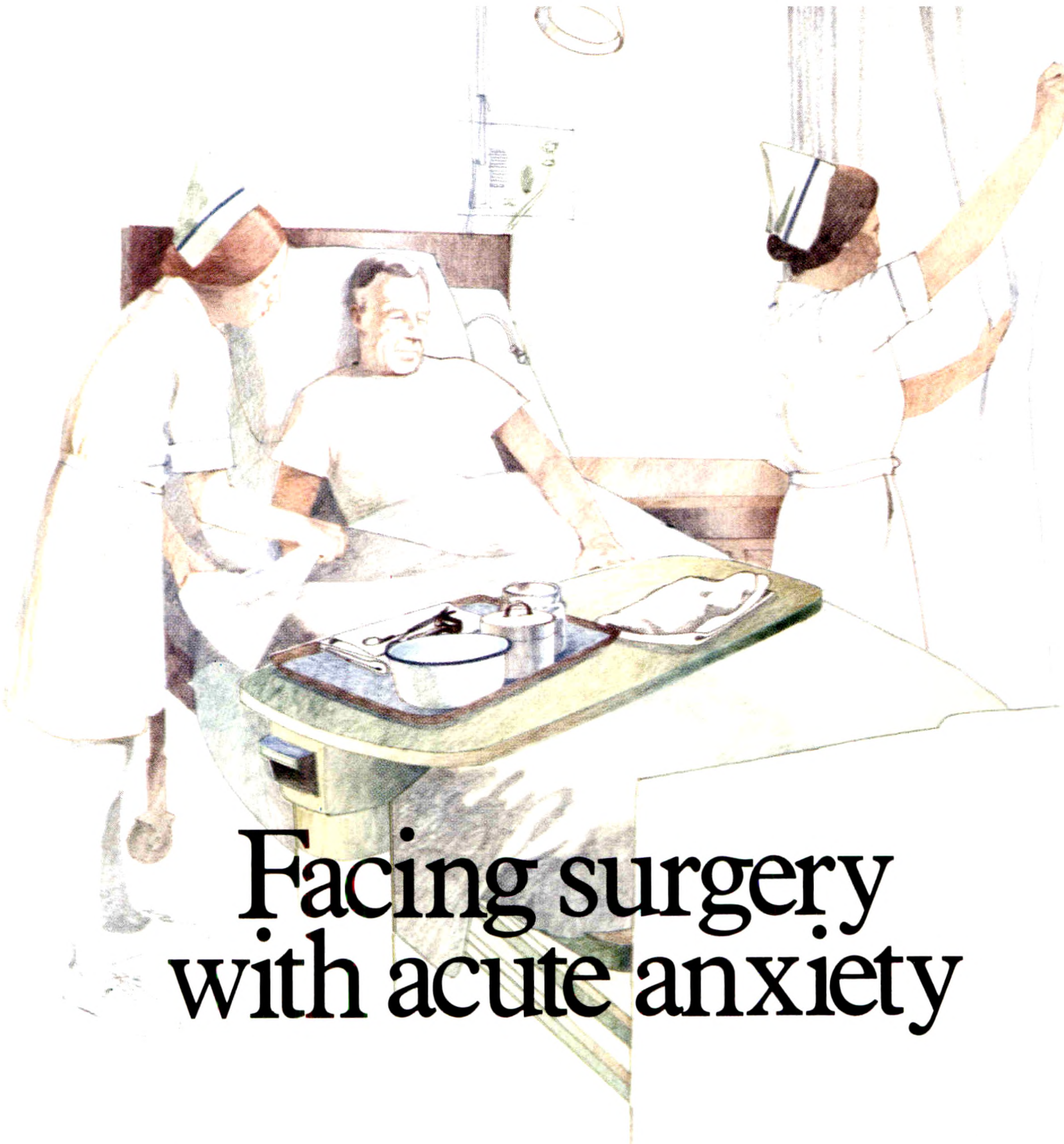
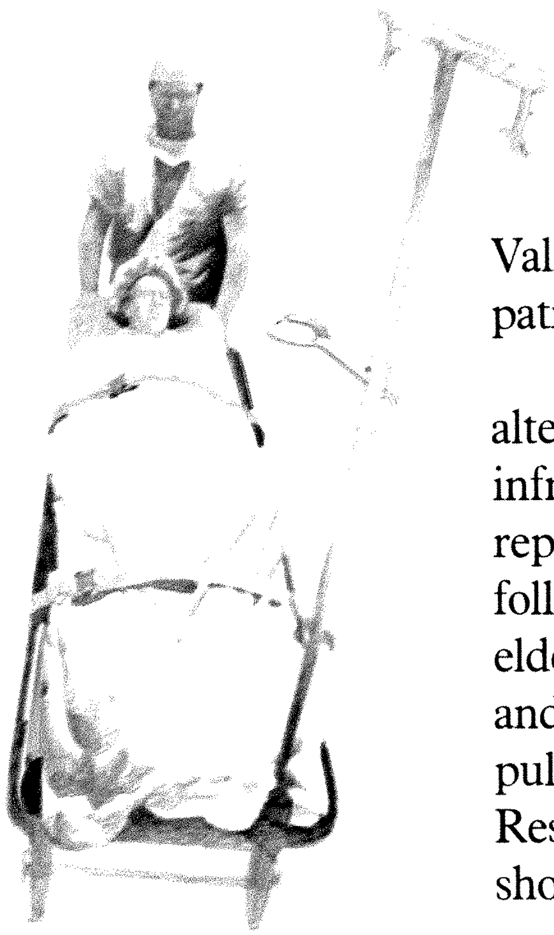
Division of G. D. Searle & Co., Chicago



Facing surgery with acute anxiety

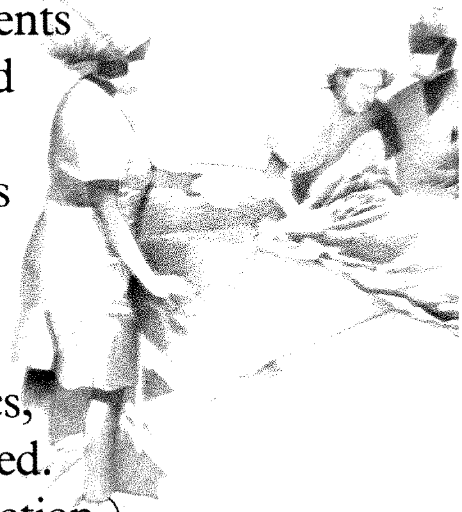
You expect your preoperative patient to be somewhat anxious and apprehensive about the scheduled surgery. But in some cases, psychic tension reaches undesirable levels as the time for the procedure approaches.

In such situations, 10 mg Injectable Valium® (diazepam), administered I.M. an hour or two before the operation, can lessen the undue anxiety and tension associated with strange surroundings and disturbing procedures. The calming effect is generally prompt and pronounced. What's more,



Valium (diazepam) can markedly reduce the patient's recall of preoperative procedures.

Injectable Valium seldom significantl alters vital signs. Nevertheless, there have bee infrequent reports of hypotension and rare reports of apnea and cardiac arrest, usually following I.V. administration, especially in elderly or very ill patients and those with limited pulmonary reserve. Resuscitative facilities should be available.



When given in conjunction with narcotics, a reduction of narcotic dosage should be considered. (See prescribing information.)

Do not mix or dilute Injectable Valium with other drugs, solutions or fluids. The 10-mg disposable syringe is especially useful in this respect, since it provides a convenient method of using Valium and at the same time helps assure aseptic handling.

Injectable Valium® (diazepam) can ease the way

ROCHE

Before prescribing, please consult complete product information, a summary of which appears on the following page.

Prior to surgery, to relieve excessive anxiety; additionally, may diminish recall

Injectable Valium® (diazepam)

ready-to-use 2-ml Tel-E-Ject® (disposable syringes)
10-ml vials
2-ml ampuls
5 mg/ml

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus and severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic and surgical procedures; cardioversion.

Contraindicated: In infants; in patients with known hypersensitivity to the drug; in acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *Inject I.V. slowly, directly into vein; take at least one minute for each 5 mg (1 ml) given. Do not mix or dilute with other solutions or drugs. Do not add to I.V. fluids.* Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, nursing women or women of childbearing potential, weigh expected benefit against possible hazard to mother and child. Not recommended for OB use.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis and phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.) Give I.V. injections slowly, directly into vein; take at least 1 minute for each 5 mg (1 ml); avoid small veins. I.M. should be by deep injection. Do not mix or dilute with other solutions or drugs. Do not add to I.V. fluids. Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 min. prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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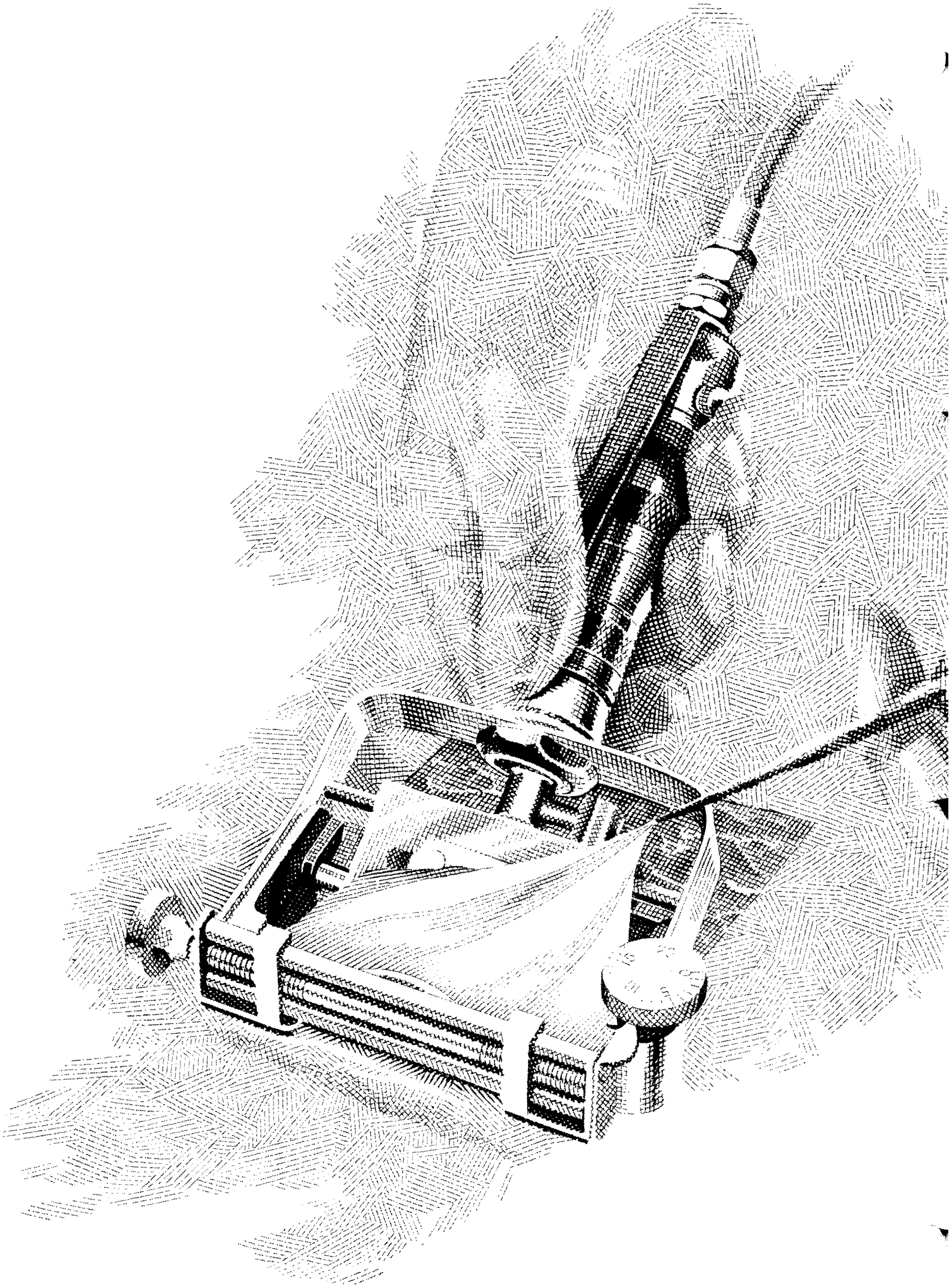

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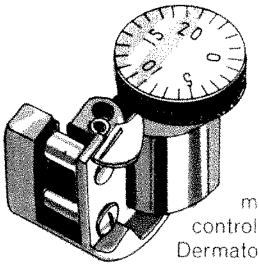

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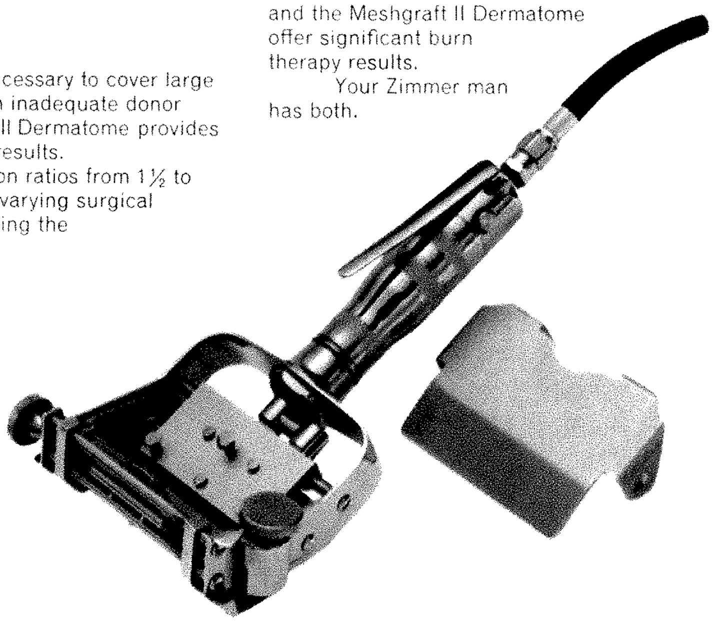

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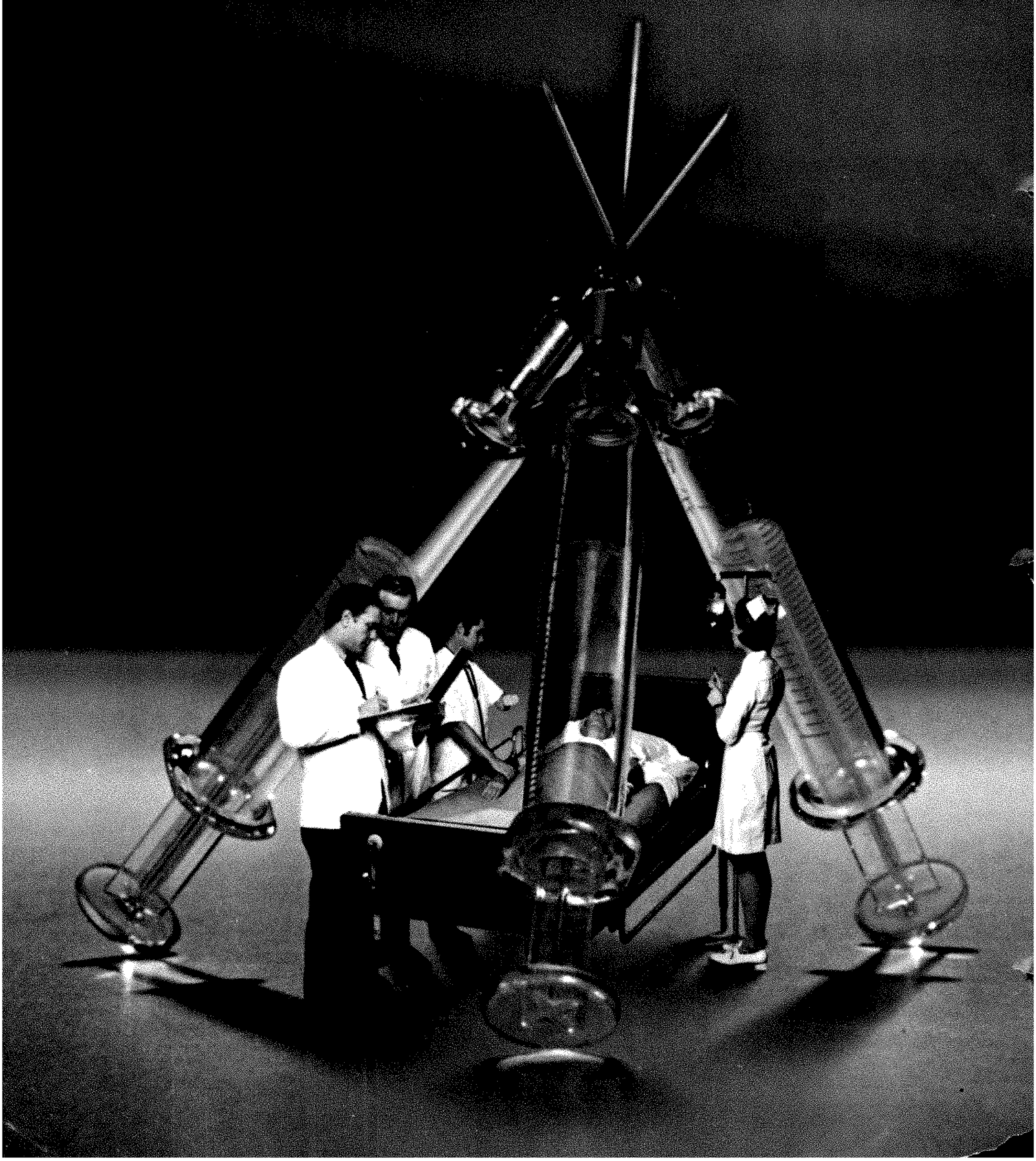
indicated for all types and degrees of moderate to severe pain with dosage that you can increase from 30 mg. to 45 mg. or 60 mg.



An analgesic as potent as you need

Type of pain	Dosage	No. patients studied	Incidence of excellent to good analgesia	Adverse Reactions
post-operative pain[1]*	**30 mg.**	29	79.3%	"As the study progressed, the dosage was increased to 45 and 60 mg. to determine whether higher doses would produce greater analgesia without an increase in adverse effects."[1] "Only a few minor side effects were observed."[1]
	45 mg.	70	83.0%	
	60 mg.	101	94.0%	
post-operative pain[2]†	**30 mg. or 60 mg.**	68	94.0%	"At the start of the study, adult patients were given 30 mg. doses. It was found, however, that a 60 mg. dose gave better analgesia with no noticeable difference in tolerance."[2]

*Study based on response to a single dose.

†Study based on multiple doses, according to patient need.

References: 1. Finestone, S. C. and Katz, J.: Pentazocine as a postoperative analgesic, *Anesth. Analg.* 45:312, May-June 1966. 2. Snow, E. W.: Pentazocine—clinical evaluation, *Abdom. Surg.* 9:150, May 1967.

Provides relief comparable to that of morphine and meperidine, but with fewer significant adverse effects††

- Compared to morphine, Talwin causes less severe respiratory depression, hypotension, urinary retention, constipation.
- Compared to meperidine, Talwin is less likely to cause nausea, vomiting, diaphoresis.

††See next page for a complete discussion of Warnings, Precautions, Adverse Reactions, and other Prescribing Information.

Injectable

Talwin® brand of **pentazocine** (as lactate)

30 mg. 45 mg. 60 mg.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, soft tissue induration, nodules, cutaneous depression, and ulceration (sloughing) at the injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.)* in boxes of 25. Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

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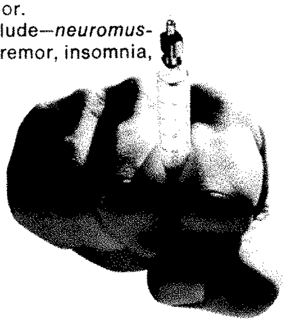
bulwark against pain
of moderate to severe intensity



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Talwin®
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pentazocine
(as lactate)

(1617)

Results of Regional Lymph Node Dissection for Melanoma

STEPHEN L. GUMPORT, M.D.,* MATTHEW N. HARRIS, M.D.†

From the Tumor Service, Department of Surgery,
New York University School of Medicine
New York, N. Y.

TWENTY YEARS AGO the results of the treatment of malignant melanoma were so poor that some specialists in the field were recommending major amputations for what we would regard today as early operable lesions of the extremities. Conventional treatment at that time was a wide excision of the primary site of the lesion. The patients were observed to see if the regional lymph nodes subsequently became enlarged. If they did, a regional lymph node dissection was then performed. Subsequently some observers felt that the regional lymph nodes should be removed electively before clinical involvement was noted.[1,3-6,11,13] Others did not agree.[14,15] The controversy still continues and this paper presents our experience with elective regional lymph node dissections and our thoughts as to their place in the treatment of malignant melanoma.

Methods

In 1949 a long-term study of malignant melanoma was initiated on the Tumor Service of the Department of Surgery at New York University Medical Center. It was not practical in this clinical setting to randomize the treatment of the patients. Therefore, a protocol was established for what was considered the optimal treatment for each patient. From that time until December, 1971, more than 800 patients with melanoma were seen and 306 regional lymph node dissections were performed. Of these, 185 patients had regional lymph node dissections done between 5 years and 20 years ago. The follow-up rate was 90%.

The patients were treated in the following manner:

1. A total excision biopsy of the melanoma was done wherever feasible.
2. After the diagnosis of melanoma was confirmed, a wide and deep re-excision of the biopsy site was performed. This usually included the fascia of the underlying muscle and closure often required the use of a split thickness skin graft.
3. Regional lymph node dissections, "in continuity" when possible, were done even when these nodes appeared to be negative clinically. Dissections were also done in instances where the nodes appeared positive clinically.

There were 6 contraindications to elective regional lymph node dissections in this study.

1. The melanoma definitely classified as superficial.
2. The melanoma arising in a freckle of Hutchinson.
3. A primary site so situated that the lymphatic drainage might be to several different groups of regional lymph nodes.
4. The presence of serious intercurrent disease.
5. The elderly patient. (About 70 years of age or older).
6. The presence of distant metastases.

With the use of these selective criteria, the operative mortality rate has been zero to the present time. They have also served to minimize the morbidity. We feel that over the years this method of selection has been of great help in improving our results of treatment. This is probably because the approach to the primary site of the tumor and its routes of lymphatic spread has been more effective. However, we are still left with the unsolved problem of the hematogenous dissemination of the disease.

Submitted for publication December 19, 1972.

* Professor of Clinical Surgery.

† Associate Professor of Clinical Surgery.

Address for reprints: Stephen L. Gumport, M.D., New York University Medical Center, 566 First Avenue, New York, N. Y. 10016.

All malignant melanomas should be staged and their depth of invasion determined. This will assist the surgeon in his choice of treatment, in making a prognosis, and later in comparing the results obtained with other patients with similar stages of the disease.

We have been impressed with the value of the classification method of Clarke in which he uses the clinical-pathological forms of the melanoma and the levels of invasion.[2,12] He divides the melanoma into 3 groups:

1. Lentigo maligna melanoma.
2. Superficial spreading melanoma.
3. Nodular melanoma.

Each of these groups has a characteristic developmental history, growth appearance and microscopic feature. The survival data may be correlated with the depth of invasion as determined microscopically. He has described 5 levels of invasion ranging from Level I where all the tumor cells are above the base membrane (*in situ* melanoma) to Level V where the subcutaneous tissues are invaded. We use these levels of depth of invasion as one of our indications as to whether elective regional lymph node dissections are performed. We do not do elective lymph node dissections for Level I or II lesions but favor them for Level III or deeper lesions.

Results

The overall error in correctly diagnosing the presence of metastases in the 306 regional lymph node dissections performed was 18%. However, in the group in which the lymph nodes were microscopically positive, and where it was particularly important that the diagnosis be made correctly, there was an error of 55%. This was due to the fact that microscopic deposits of metastatic disease in the regional lymph nodes were not palpable. In 232 cases the nodes were microscopically negative and of these 15 were called positive clinically, an error of 6%. (Table 1).

When considering the error of clinical judgement by site in the group of patients with microscopically positive nodes in the groin the error was 50%, in the axilla 60% and in the neck 65%.

Of the 306 regional lymph node dissections, 185 of them were performed 5–20 years ago. It should be particularly noted that there was a 90% follow-up of these patients and that all patients dead from any cause whatsoever or lost to follow-up were counted as if they died from melanoma. The figures were calculated in this manner in order to be as conservative as possible in determining the overall results of surgical therapy. With this in mind, it was found (Table 2):

1. When the surgeon thought the regional lymph nodes were negative clinically and after removal they were reported by the pathologist on random sections to be negative, 56% of these patients were alive and well 5 or more years after their treatment.

TABLE 1. *Error of Clinical Judgement*

232 Cases Nodes Were Microscopically Negative of these, 15 were Called Positive Clinically	Error 6%
74 Cases Nodes Were Microscopically Positive of these, 41 were Called Negative Clinically	Error 55%
	Total Overall Error 18%

2. When the surgeon thought these regional lymph nodes were positive clinically, and, after removal they were reported to be negative microscopically, 27% of these patients were alive and well five years or more. This lower survival rate with microscopically negative nodes might be due to the fact that some of the nodes were actually microscopically positive though they were reported as negative, as only random sections were taken.
3. When the surgeon thought that the regional lymph nodes were negative clinically, and they were reported as being microscopically positive, 30% of these patients were alive and well 5 years and more after their treatment. While this figure is only half the percentage of patients in the clinically-negative, microscopically-negative group, it is still 3 times the percentage in the group where the nodes were clinically and microscopically positive (10%).
4. When the surgeon thought that the regional nodes were clinically positive and they were reported as being microscopically positive, only 10% of the patients were alive and well five years or more after definitive surgery.

The operative techniques used in these regional node dissections and their complications have been previously described.[7,8,10] The 306 regional lymph node dissections discussed in this paper have been performed with no operative mortality and a low morbidity rate.

Discussion

The fact that only 10% of patients were alive and well 5 or more years after their regional lymph nodes were removed when these were already both clinically involved and microscopically involved, supports the impression that there is a hazard in waiting for these nodes to become grossly positive before removing them.

Many observers feel that elective regional lymph node dissections should be done, but a controlled study has not yet been found feasible and there is no unanimity of opinion on this point. Charalambidis and Patterson[1] reported on a series of 250 patients treated at the Pondville Hospital between 1928 and 1959 with elective regional lymph node dissections. They said that when the lymph nodes were clinically and histologically free of tumor "74.8 per cent, survived 5 years or more. With invasion

TABLE 2. *Results of Regional Node Dissections (185 Cases Operated Over 5 Years Ago)*

	L & W	Ill with recur.	Lost	Dead*	Total
Nodes Microscopically Negative	Clin. ⊖ 69 (56%)	6 (5%)	12 (10%)	37 (30%)	124
	Clin. ⊕ 3 (27%)	0	2 (18%)	6 (55%)	11
Nodes Microscopically Positive	Clin. ⊖ 6 (30%)	2 (10%)	1 (5%)	11 (55%)	20
	Clin. ⊕ 3 (10%)	0	3 (10%)	24 (80%)	30
					185

* Death from all causes

of the lymph nodes, the prognosis in melanoma drops drastically." They felt that "by excising the nodes, one of the sources of recurrence of the disease in the near or far future is eliminated."

Conley and Pack[3] reported on 175 patients with melanoma of the head and neck region. They felt that for infiltrating melanomas of the scalp, mucous membrane, the neck and the ear there was "a great proclivity for regional metastasis," and they recommended resection of the primary site in continuity with the regional lymph nodes electively except for midline lesions. Fortner, Booher and Pack[4] reported on 220 patients who had groin dissections for melanoma performed at Memorial Hospital between 1931 and 1956. They concluded that "the concept of elective node dissection is valid."

Goldsmith, Shah, and Kim[5] reviewed 1485 cases of melanoma seen at Memorial Hospital between 1950 and 1965 and studied until 1970. They concluded that "the best form of treatment for patients with malignant melanoma is a wide excision of the primary lesion in association with a routine lymph node dissection, regardless of the clinical status of the lymph nodes." They further stated that "if one elects not to perform a lymph node dissection for non-palpable lymph nodes, a sizable proportion of patients in this group will have histologic foci of melanoma in their retained lymph nodes." In their series this figure was 17% (50/296) and in our present series 14% (20/144). They further stated that "electing to permit 1 out of every 5 or 6 patients to retain lymph nodes that harbor microscopic melanoma is a decision which is difficult to justify." Gumport and Meyer[6] in 1959 reviewing 126 cases of malignant melanoma 5 or more years since their definitive treatment at New York University Medical Center, concluded that the best results were obtained when an elective regional lymph node dissection was performed in addition to a wide and deep excision of the primary site of the lesion.

Lane, Lattes and Malm[9] in 1958 reported on the results of their study of 117 patients treated at Presbyterian Hospital where the surgical specimens were very carefully studied in the Surgical Pathology Laboratory and *serial* sections of the lymph nodes performed. "Metastatic deposits were found in a significant proportion (42%) of so-called prophylactic lymph node dissections." This figure obtained by these serial section examinations is probably a much more accurate assessment of the actual incidence of involvement of the electively removed lymph nodes than the lower figures cited above by Goldsmith and also by Gumport, which were obtained on random sections of electively removed lymph nodes.

McSwain *et al.*[11] in 1964 reported on 203 patients with malignant melanoma. They too concluded that elective regional lymph node dissections "were a justifiable procedure" and they performed these unless the melanoma was a small and superficial one or the lymphatic drainage of the part could be to several groups of regional lymph nodes.

Moore and Gerner[13] in 1970 at Roswell Park took an in-between position and felt the question as to the value of elective regional node dissections had not yet been settled. They felt it was not incongruous to recommend prophylactic neck dissections for lateral lesions of the head and neck and axillary dissections for lesions of the upper arm but expressed reservations about superficial or radical groin dissection.

There are surgeons who feel that they have demonstrated little benefit from elective lymph node dissections done routinely. In this connection Polk and his coworkers[14,15] have concluded by means of a mathematical formula that "analysis of comparable patients harmed and helped by routine practice of elective regional lymphadenectomy for melanoma indicates such slight net benefit as to preclude its extensive use." We agree with Dr. Polk that this procedure should not be done routinely but the patients should be carefully selected. We disagree with him in equating "harmed" meaning operation and its attendant morbidity with "helped" which means the actual saving of a patient's life who has non-palpable but microscopically involved regional lymph nodes.

Conclusions

1. There is an appreciable error (18%) in clinically evaluating the presence of metastases in regional lymph nodes of patients with malignant melanoma.

2. Contraindications to elective regional lymph node

dissection for patients with malignant melanoma have been described.

3. There appears to be an advantage for some patients with invasive malignant melanoma when elective regional lymph node dissections are performed in a selective manner.

Summary

The results of regional lymph node dissections in 306 patients performed since 1949 have been reviewed. The follow-up rate has been 90%. Contraindications to elective regional lymph node dissections are set forth. It was found that clinical estimates of the microscopic involvement of regional lymph nodes were subject to an error of 18%.

There was a zero mortality rate and a low morbidity rate in the performance of these regional lymph node dissections.

It appears from this study that it is not possible to accurately identify preoperatively by palpation those patients in whom the regional lymph nodes contain metastatic deposits of melanoma. Only 10% of the patients with grossly positive lymph nodes and microscopically positive lymph nodes will have a long-term survival. It would therefore seem that there is benefit to be obtained at small risk to the patient from elective regional lymph node dissections performed selectively for invasive melanoma.

Acknowledgments

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References

1. Charalambidis, T. and Patterson, W. B.: A Clinical Study of Two Hundred and Fifty Patients with Malignant Melanoma, Surg. Gynec. Obstet., **115**:333, 1962.
2. Clark, W. H. Jr., Lynn, F., Bernardino, E. A. and Mihm, M. C.: The Histogenesis and Biologic Behaviour of Primary Human Malignant Melanomas of the Skin. Cancer Res., **29**:705, 1969.
3. Conley, J. and Pack, G. T.: Melanomas of the Head and Neck. Surg. Gynec. Obstet., **116**:15, 1963.
4. Fortner, J. G., Booher, R. J. and Pack, G. T.: Results of Groin Dissection for Malignant Melanoma in Two Hundred and Twenty Patients. Surgery, **55**:485, 1964.
5. Goldsmith, H. S., Shah, J. T. and Kim, D. H.: Prognostic Significance of Lymph Node Dissection in the Treatment of Malignant Melanoma. Cancer, **26**:606, 1970.
6. Gumport, S. L. and Meyer, H. W.: Treatment of One Hundred and Twenty Six Cases of Malignant Melanoma: Long-Term Results. Ann. Surg., **150**:989, 1959.
7. Harris, M. N., Gumport, S. L., Berman, I. R. and Bernard, R. W.: Ilioinguinal Lymph Node Dissection for Melanoma. Surg. Gynec. Obstet., **136**:33, 1973.
8. Harris, M. N., Gumport, S. L. and Maiwandi, H.: Axillary Lymph Node Dissection for Melanoma. Surg. Gynec. Obstet, **135**:936, 1972.
9. Lane, N., Lattes, R. and Malm, J.: Clinicopathological Correlation in a Series of One Hundred Seventeen Malignant Melanomas of the Skin of Adults. Cancer, **11**:1025, 1958.
10. Martin, H., DelValle, B., Ehrlich, H. and Cahan, W. G.: Neck Dissection. Cancer, **4**:441, 1951.
11. McSwain, B., Riddell, D. H., Richie, R. E. and Crouker, E. F.: Malignant Melanoma: A Report of Two Hundred and Three Patients. Ann. Surg., **159**:967, 1964.
12. Mihm, M. C., Clark, W. H., Jr. and From, L.: The Clinical Diagnosis, Classifications and Histogenic Concept of the Early States of Cutaneous Malignant Melanomas. New Engl. J. Med., **284**:1078, 1971.
13. Moore, G. E. and Gerner, R. E.: Malignant Melanoma. Surg. Gynec Obstet., **132**:427, 1971.
14. Polk, H. C., Jr., Cohn, J. D. and Clarkson, J. C.: An Appraisal of Elective Regional Lymphadenectomy for Melanoma. *In* Current Topics in Surgical Research. Vol. 1. New York, Academic Press, Inc., 1969.
15. Polk, H. C., Jr. and Linn, B. S.: Selective Regional Lymphadenectomy for Melanoma: A Mathematical Aid to Clinical Judgement. Ann. Surg., **174**:402, 1971.

Transplantation of Fetal Intestine:

Survival and Function in a Subcutaneous Location in Adult Animals

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ALTHOUGH TRANSPLANTATION of fetal intestinal tissue has been carried out successfully in a variety of experimental animals, no data is available concerning the physiological function of such transplants.

In 1971, Zinzar *et al.*[14] reported that fetal intestine, when transplanted subcutaneously into an adult syngeneic host, would "grow progressively and form organlike cavities." They indicated that the fetal transplant, although initially devoid of a blood supply in the host, would become vascularized, and remain as differentiated intestinal tissue.

Our attention was drawn to this study because of our research in the field of tumor angiogenesis. The mechanism of tumor vascularization, and the possible control of solid tumors by the blockade of angiogenesis has been the primary interest of this laboratory.[3–5] Tumor implants stimulate continuous proliferation of new capillary endothelium through the release of a diffusible material, which has been termed tumor angiogenesis factor, (TAF). Normal tissues, with but one or two possible exceptions, lack this property. Although fetal tissues can be vascularized rapidly, it is not yet clear whether they can stimulate neovascularization.

We have found that transplanted fetal gut can be made to grow as a longitudinal tube with a continuous lumen. In addition, our studies have shown that this transplant absorbs amino acids, glucose, and fat, maintains peristalsis, and exhibits normal brush border enzyme activity. These findings suggest a potential application for this system: a simple method for the transplantation and subsequent use of an accessory intestine in infants dying from a short-bowel syndrome.

Methods and Materials

A. Transplantation Technique. All transplantation experiments were done with syngeneic animals. Female Fisher strain rats* (40–50 grams) were used as recipients. Donor fetuses from the same strain were delivered by Caesarian section between the 18th to the 21st day of gestation.

The gastrointestinal tract from the stomach to the descending colon was removed *en bloc* from the fetus and stripped of its mesentery. The stomach and large bowel were discarded, and the remaining small intestine (the approximate calibre of a #0 silk suture) was flushed

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with cold Ringer's lactate solution to remove meconium and other particulate matter.

Under light ether anesthesia and with sterile technique, an air sac was formed on the dorsal surface of each recipient animal, and a longitudinal incision to the left of the midline was made in the sac. The fetal intestine from mid-jejunum to distal ileum was stretched along the midline and sutured in place at the cranial and caudal ends. The skin was closed with Michelle clips and the animals returned to their cages. No attempt was made to separate the recipients in separate cages.

A total of 160 rats received a subcutaneous fetal intestine. Of these, 120 had tubes of intestine that were acceptable for further experimentation. The remaining rats had small pieces of intestine that had either failed to grow or had formed large cysts because of improper placement in the subcutaneous space. These animals were used as controls for the studies described below.

B. Gross and Histologic Examinations. One animal was sacrificed every day for the first week and then at intervals of 2–3 days for 8 weeks. The subcutaneous space was opened, the diameter and length of the intestinal implant were measured, and frequency of peristalsis was observed. Specimens were preserved in formalin, and histologic sections were prepared from paraffin blocks and stained with hematoxylin and eosin by standard techniques.

C. Absorption Studies. Studies of absorption of glucose, amino acids, and a long-chain, fatty acid were carried out in 50 animals. Of this number, 23 rats had transplanted intestine and 27 were control animals. All perfused, subcutaneous fetal intestines had been in place for 21 days post-transplant. All control animals were 100–120 grams (4–6 weeks-old). The animals were not fasted prior to an absorption study.

Under light ether anesthesia, the subcutaneous intestine was carefully and completely cleared of a thick, pasty-yellow material that could be removed by forceps and/or saline irrigation. Glass cannulae were introduced at either end of the intestine and secured with sutures. The intestine was again irrigated with saline to identify leaks.

The intestinal transplant was perfused by a recirculation technique through its lumen at 0.2 to 0.3 ml/minute with a continuous flow pump* for 5 hours (Fig. 1). The total volume for each perfusion was 10 ml. at room temperature. An initial equilibration period of 30 minutes was allowed. Throughout the 5-hour period, the animal was kept warm with a heating lamp.

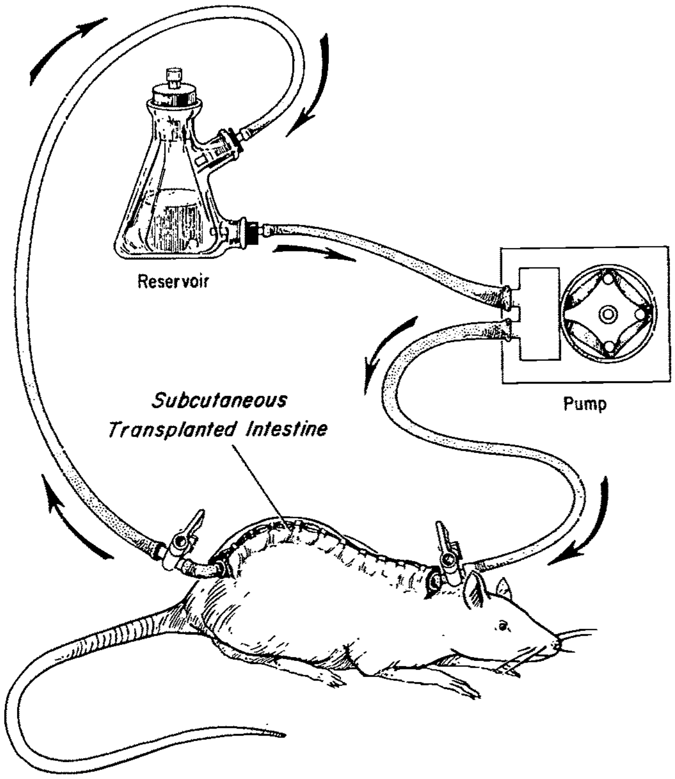

FIG. 1. Model for perfusion of subcutaneous intestine.

Radioactive tracers,† ^{14}C-3-O-methyl glucose (specific activity 18.5 mC/mM), ^{14}C-glycine (specific activity 91 mC/mM), and ^{14}C-oleic acid (specific activity 56.3 mC/mM) were tested individually for absorption. All tracers, except oleic acid, were added to their respective, unlabelled stock solutions which were prepared as a 5mM concentration in phosphate buffered saline. Total radioactivity added to the stock solution was 1μC/10ml. perfusate. All perfusates (except oleic acid) also contained a 5mM mannitol solution with a ^{3}H-mannitol marker (specific activity 2.65 C/mM) added as 5μC/10ml. perfusate. Since mannitol is not actively absorbed (10), it served as an internal control for water flux and loss of test substance by processes other than active absorption. Oleic acid was prepared as an 8.8mM concentration in a micellar solution of monoolein (5mM) and sodium taurocholate (40mM).* The final osmolarity of all solutions was 290–300 mOsms, and the pH range was 7.1 to 7.3.

Duplicate samples were removed as 0.1 ml. aliquots from the reservoir at 0, ½, 1, 1½, 2, 3, 4, and 5 hours. Samples were then counted in 10 cc. of Bray's solution in a Packard liquid scintillation spectrometer. Correction of quenching was made by the external standard method; results were converted to disintegrations/minute for all calculations. The amount of substance absorbed was measured by the disappearance of counts from the reservoir and is expressed by the equation:

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* Holter Company, Division of Estracorpored MED Spec., Inc., Mt. Laurel, New Jersey.

† New England Nuclear Company, Boston, Massachusetts.

* Prepared by Dr. Robert Glickman, Gastrointestinal Unit, Massachusetts General Hospital, Boston, Massachusetts.[6]

μ moles absorbed/cm.

$$= \frac{\{1 - (\mathrm{dpm}_f/\mathrm{dpm}_i)\}\ (\mathrm{Man\ R})\ (\mathrm{Ci})\ (V_c)}{\mathrm{cm.\ intestine}}$$

Where: dpm_f and dpm_i are the final and initial disintegrations/minute of test substance.

Man R = $\mathrm{dpm}_f/\mathrm{dpm}_i$ for mannitol. C_i = concentration of test material in μ moles/ml., and V_c = circulated volume in milliliters during each time period, corrected for sampling. Statistical analyses were performed using the standard Student's two-tailed "t" test.

Control absorption studies on rats of the same strain were conducted by perfusing a proximal jejunal loop *in situ*. Proximal jejunal loops were of the same length and were perfused in exactly the same manner as were the subcutaneous intestines. All animals were sacrificed after an absorption experiment.

D. Disaccharidase Activity. Five subcutaneous intestinal transplants and jejunal segments from three control animals of the same strain and age were removed, opened longitudinally, and the mucosa scraped on an iced glass plate with a glass slide. The tissue was then homogenized in 30 volumes of iced 5mM EDTA, pH 7.4. The disaccharidase activity was assayed by a modification[7] of the method of Messer and Dahlqvist.[9]

Results

A. Gross and Histological Examinations. In the first 24 hours, the transplant became visibly hemorrhagic and the lumen filled with extravasated blood. When the gut was observed grossly at this time, it looked dark and ischemic.

Within the next 3 days, an areolar membrane covered the intestine causing it to adhere to the underlying dorsal fascia. On day three, the normal layers of the intestine were histologically identifiable, and villi and ganglion cells were seen. Extravasated blood remained in the submucosa, and this layer was relatviely thick when compared to the others. The gut looked pink and viable by the fourth day. Large veins segmentally drained the intestine. The wall of the gut was thick and a muscular coat was identifiable. Microscopically, (Fig. 2) the villi were prominent and the epithelial cells columnar. Goblet cells were present. The intraluminal contents appeared more dense and reduced in volume. By the seventh day, small cysts developed at either end of the intestine, and the gut increased in length by approximately ½ centimeter.

During the next 2–3 weeks, the intestine continued to increase its length to an average of 4–6 cm. In the third week, one could see a straight, vascularized intestinal tube. The diameter of the tube at this time was large enough to admit readily a 3 mm. cannula. Light microscopy showed normal structures. Figure 3 demonstrates normal architecture in an intestine 21 days post-transplant. The higher power view of 25 day post-transplanted gut (Fig. 4) shows normal villi and crypts. In some histologic sections, Peyer's patches were identified. The longitudinal and circular muscle bands with accompanying intermyenteric plexi were also seen.

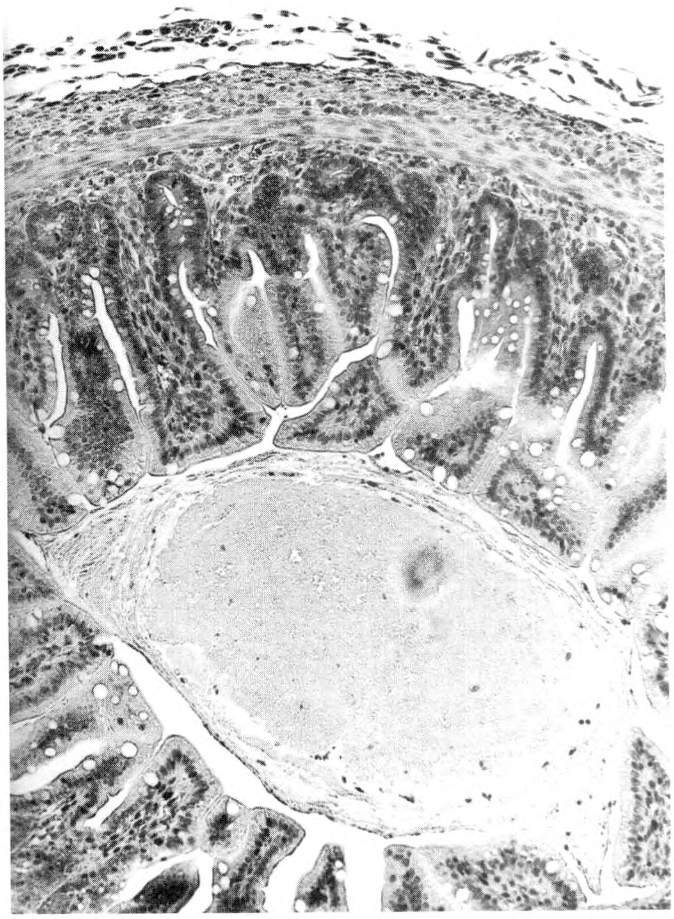

FIG. 2. Fetal small intestine 4 days after transplantation (× 187). Note normal goblet cells, intermyenteric ganglia, and muscular layers.

Transplants were followed for as long as 8 weeks. The diameter of the gut continued to increase as more material was deposited within the lumen. The length continued to increase in proportion to the growth of the animal.

The intraluminal material, made up of desquamated cells and mucous, became yellow in color after the first week. It had a very tenacious character and was exceedingly difficult to remove from the lumen after the second week. Because of its continued accumulation in the obstructed intestine, pressure increased intraluminally, and if the substance was not removed, histologic changes such as flattened, cuboidal epithelial cells and blunted villi resulted.

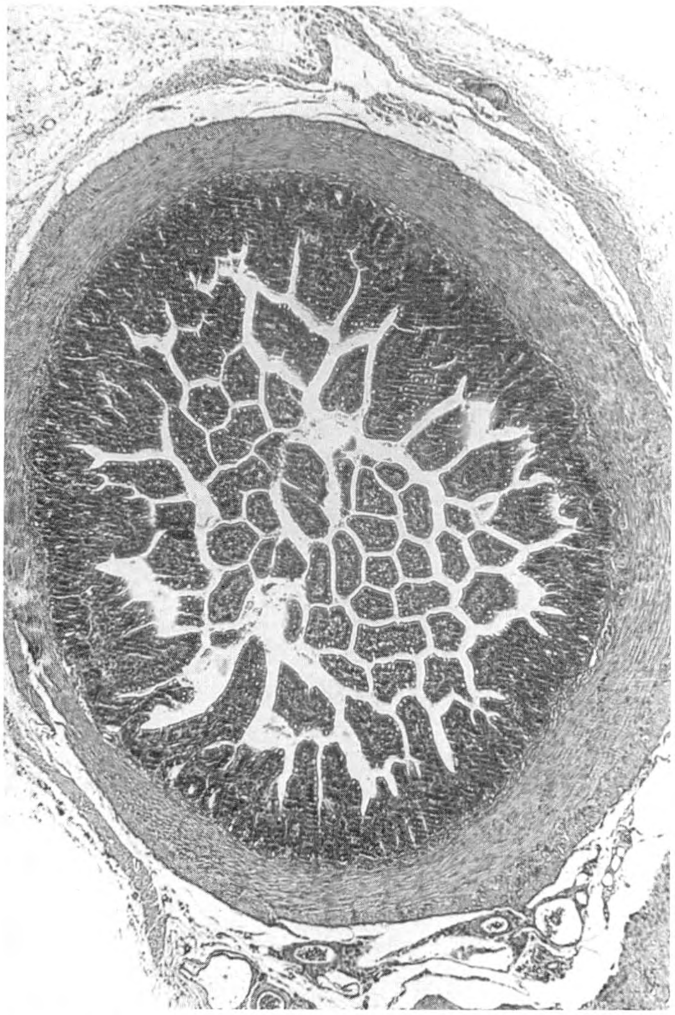

FIG. 3. Fetal small intestine 21 days after transplantation (×46.8).

B. Absorption Studies. A non-metabolizable simple sugar, ^{14}C-3-O-methyl glucose, was recirculated through the intestinal transplants and controls for 5 hours. In the first 2 hours, the control intestine absorbed significantly more glucose than did the transplant ($p < 0.02$). The difference in absorption between the transplant and the control during the third, fourth, and fifth hours was not significantly different ($p > 0.05$). The results of these studies are shown in Fig. 5.

Amino acid absorption studies were done with both glycine and α-aminoisobutyric acid (a non-metabolizable neutral amino acid). The absorption curves for glycine (Fig. 6) have similar slopes, but the amount absorbed was always, but not significantly, greater in the control intestines. The transplanted intestines did not absorb α-aminoisobutyric acid. Control intestines, however, showed absorption of this analogue in quantities comparable to results published by others.[12]

Fat absorption was examined in only one transplanted intestine and one control animal (Table 1). Oleic acid, a long-chain, unsaturated fatty acid, was perfused in a micellar preparation for 5 hours. At the end of 5 hours, oleic acid was absorbed in similar amounts by both the control and experimental intestine.

C. Disaccharidase Activity. Disaccharidase activity (Table 2) was measured in the transplanted intestine and in comparably aged controls of the same strain. Lactase activity in the 3–week-old transplanted intestine was slightly higher than that in controls. Maltase and sucrase activities were significantly higher in the control intestines (from 3–week-old and adult animals) than in the transplanted gut.

D. Peristalsis. Contractions in the smooth muscle were consistently noted in the transplants after the second week. The contractions seemed unidirectional and propulsive in nature. Stimulation by local application of neostigmine* (0.2 mg/ml) increased the activity of the muscularis, and on one occasion, a transplanted intestine was able to evacuate its entire intraluminal contents by propulsive, forceful, peristaltic contractions.

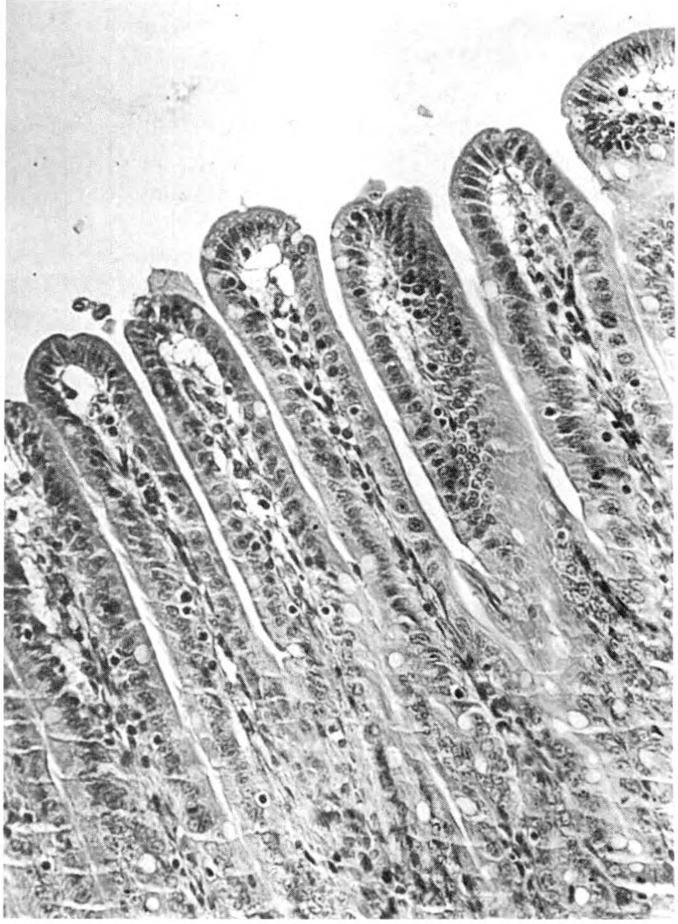

FIG. 4. Fetal small intestine 25 days after transplantation (× 468). Note normal villi and crypts.

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* Elkins-Sinn, Inc., Cherry Hill, New Jersey.

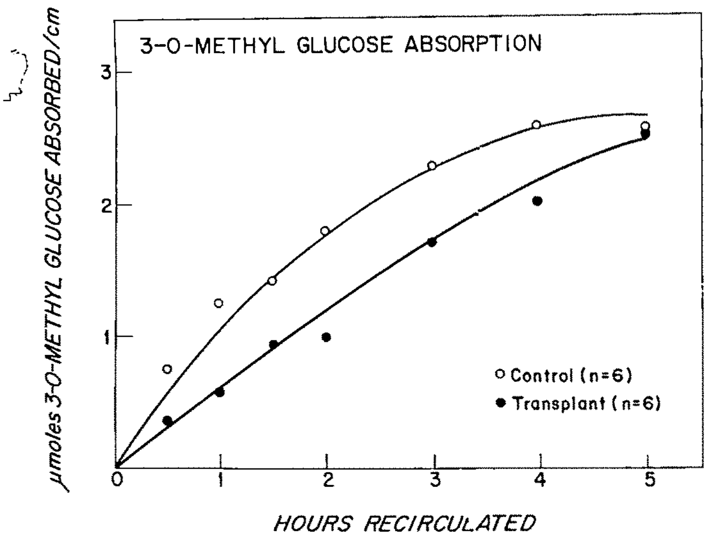

Fig. 5. ^{14}C-3-O-methyl glucose absorption curves for transplanted and control intestine.

Discussion

These studies show that free, syngeneic transplants of fetal gut into adult animals will vascularize, grow, retain peristalsis, and absorb nutrients. They maintain histological integrity, produce brush border enzymes, and exhibit ganglia and Peyer's patches.

Fetal transplants, both homologous and heterologous, survive and become vascularized in 3–4 days. Greene[8] demonstrated that stomach, small bowel, kidney, brain, lung, skin, and cartilage vascularized in the anterior chamber of the rabbit eye and remained as histologically differentiated tissues. Toolan[13] transplanted minced fetal intestine to the anterior chest wall of rabbits. These grafts remained viable for as long as 3 months if the homologous recipients were irradiated or treated with cortisone. Baxter and Goldstein[2] transplanted fetal human skin to burn patients, but noted rejection of the grafts within 46 days. Heterografts of human fetal lung and kidney have been transplanted into thymectomized, A.L.S.-treated mice. These tissues survived up to 28 days, but when intestine was transplanted into the same system, the grafts never grew.[11]

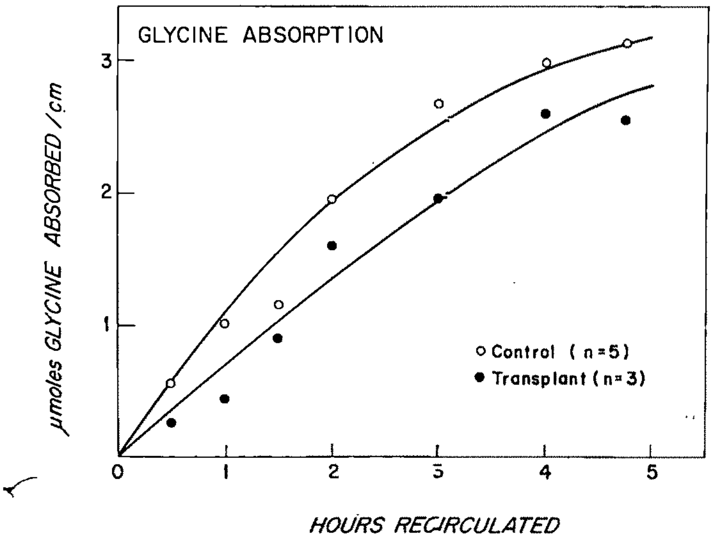

Fig. 6. ^{14}C-Glycine absorption curves for control and transplanted intestine.

Table 1. *Fat Absorption*
(*μ moles oleic acid absorbed per centimeter intestine*)

Time (hours)	Transplant	Control
½	1.99	0.92
1	4.30	2.28
1½	4.22	2.95
2	4.70	3.29
3	4.93	4.06
4	4.69	4.87
5	5.11	5.43

Recently, Barakat and Harrison[1] demonstrated that fetal kidney, transplanted subcutaneously into homologous rats survived and functioned. Their homografts survived up to 6 weeks, but succumbed to a pressure necrosis presumably by a mechanism like that of a closed hydronephrosis.

Our studies indicate that fetal intestine removed just before term and transplanted subcutaneously into a syngeneic host attains a normal histological appearance, grows linearly in proportion to the growth of the animal, and is capable of active peristalsis, all as a result of successful vascularization. Although the current experiments do not provide information regarding the mechanization of vascularization in transplanted fetal tissue, they do not represent a model system in which this can be evaluated.

The present experiments also demonstrate that func-

Table 2. *Disaccharidase Activity*
(*μ moles glucose released/min./mg. protein*)

Animal	Lactase	Maltase	Sucrase
Transplant 1	.050	.142	.048
Transplant 2	.035	.249	.058
Transplant 3	.041	.344	.043
Transplant 4	.025	.186	.021
Transplant 5	.021	.201	.038
Mean ± SE =	.034 ± .005	.224 ± .034	.042 ± .006
Control 1 (3-weeks-old)	024	.384	.087
Control 2 (3-weeks-old)	.024	.370	.082
Control 3 (3-weeks-old)	.020	.353	.082
Mean ± SE =	.024 ± .001	.369 ± .009	.084 ± .001
Control (4–6 weeks old)*			
Mean ± SE =	.026 ± .001	.451 ± .070	.087 ± .005

* (n = 4), values customarily obtained for rats in this laboratory.[7]

tional characteristics of the normal fetal intestine and their developmental changes survive after transplantation. At 21 days post-transplant, lactase activity is at a level comparable to that in normal animals, although sucrase and maltase levels are somewhat lower than normal. This confirms the histological evidence that the microvillus membrane is intact in the transplant. Glycine and glucose absorption are also nearly normal, although alpha-aminoisobutyric acid is not absorbed. The reason for this failure is not clear at present, but it may represent subtle biochemical defects after transplantation which might become normal later. The studies of oleic acid absorption from a micellar solution suggest that the uptake capacity of the transplanted epithelial cells is normal. We can not comment upon the utilization or disposal of the absorbed fat, since we have not yet studied the lymphatic drainage of the transplants. Presumably, uptake into the circulation of this long-chain fatty acid would require intact lymphatics.

We have recently carried out further experiments in rats which show that the transplanted intestine can be anastamosed to the recipient gut *in vivo*, and that the animal continues to thrive. These experiments will be reported separately.* It seems possible, therefore, that a similar procedure might be feasible clinically, and that a closely matched intestine from an aborted human fetus could be placed subcutaneously in a child who lacks enough bowel for survival. Since a vascular anastamosis is not required, it may greatly simplify the approach to intestinal transplantation.

Summary

Fetal rat intestine was transplanted into the subcutaneous space of a syngeneic host. The transplant was able to establish a blood supply, grow progressively, and exhibit normal histology. Studies were done to examine absorption, brush border enzymes, and peristalsis. Glucose, glycine, and oleic acid were absorbed. Peristalsis was present, and disaccharidase activity was exhibited. Clinical implications are discussed.

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We are indebted to Dr. Michael Field for helpful suggestions, and to Ms. Stephanie Jaksina for her valuable help. We thank Ms. Christine Keller and Ms. Alison Mulhearn for the histologic preparations and Messrs. Paul Wesley, Frank Robinson, Scott Eder, and John Tountas for their technical assistance.

Addendum

Since the submission of this manuscript, similar data regarding morphology and the development of disaccharidase activities in transplanted mouse intestine have appeared (Ferguson, A., Gerskowitch, V. P. and Russell, R. I., gastroenterology, 64:292, 1973).

References

1. Barakat, T. I. and Harrison, R. G.: The Capacity of Fetal Neonatal Renal Tissues to Regenerate and Differentiate in a Heterotopic Allogeneic Subcutaneous Tissue Site in the Rat. J. Anat., **110**:393, 1971.
2. Baxter, H., Goldstein, M. and McMillan, G. C.: The Fate of Human Fetal Homo- and Heterografts. Plast. Reconstr. Surg., **22**:516, 1958.
3. Folkman, J., Merler, E., Abernathy, C. and Williams, G.: Isolation of a Tumor Factor Responsible for Angiogenesis. J. Exp. Med., **133**:275, 1971.
4. Folkman, J.: Anti-Angiogenesis: New Concept for Therapy of Solid Tumors. Ann. Surg., **175**:409, 1972.
5. Gimbrone, M. A., Leapman, S. B., Cotran, R. S. and Folkman, J.: Tumor Dormacy in Vivo by Prevention of Neovascularization. J. Exp. Med., **136**:261, 1972.
6. Glickman, R. M., Kirsch, K. and Isselbacher, K. J.: Fat Absorption During Inhibition of Protein Synthesis: Studies of Lymph Chylomicrons. J. Clin. Invest., **51**:356, 1972.
7. Grand, R. J., Chong, D. A. and Isselbacher, K. J.: Intracellular Processing of Disaccharidases: the Effect of Actinomycin D. Biochim. Biophys. Acta, **261**:341, 1972.
8. Greene, H. S. N.: The Heterologous Transplantation of Embryonic Mammalian Tissues. Cancer Res., **3**:809, 1943.
9. Messer, M. and Dahlqvist, A.: A One-Step Ultramicro Method for the Assay of Intestinal Disaccharidases. Anal. Biochem., **14**:376, 1966.
10. Miller, D. L. and Schedl, H. P.: Total Recovery Studies of Nonabsorbable Indicators in the Rat Small Intestine. Gastroenterology, **58**:40, 1970.
11. Phillips, B. and Gazet, J. C.: Growth of Human Foetal Tissue in Mice Treated with Antilymphocyte Serum. Nature, **222**:1292, 1969.
12. Schedl, H. P., Miller, D. L., Wilson, H. D. and Flores, P.: Aminoisobutyric Acid Transport and Tissue Concentration at Various Intestinal Sites. Am. J. Physiol., **216**:1131, 1969.
13. Toolan, H. W.: Growth of Embryonic Gut and Stomach on the Exterior Chest Wall of Adult Cortisone-treated Homologous Hosts. Cancer Res., **17**:707, 1957.
14. Zinzar, S. N., Leitina, B. I., Tumyan, B. G., Svet-Moldavsky, G. J.: Very Large Organ-like Structures Formed by Syngeneic Foetal Alimentary Tract Transplanted as a Whole or in Parts. Rev. Europ. Etudes Clin. et Biol., **16**:455, 1971.

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* Deutsch, A., Leapman, S., Folkman, J. Unpublished data.

Pelvic Neuroblastoma:

A Better Prognosis

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NEUROBLASTOMA is the commonest tumour of childhood derived from neural crest ectoderm. It may occur at any site in which such tissue existed in the embryo. The tumour most commonly arises in the adrenal medulla and associated sympathetic ganglia, but may originate in the neck, thorax or pelvis.

In children's centres about 10% of malignant neoplasms are neuroblastoma.[1,6] One hundred and eighty four tumours arising from the sympathetic nervous system (neuroblastoma 165, ganglioneuroma 18 and phaeochromocytoma 1) were seen at the Hospital for Sick Children London, between 1925 and 1962 inclusive.[3] In this period 1,800 patients with malignant tumours were treated; leukaemia accounted for 36%, intracranial neoplasms 25%, neuroblastoma 10% and nephroblastoma 7.5%. The present series describes 7 children with pelvic neuroblastoma who were treated at the Hospital for Sick Children, between 1950 and 1972. Five of these children were described briefly, in relation to vitamin B_{12} therapy but with limited follow-up, in an earlier report by Bodian.[3] Children who had predominantly abdominal tumour but with pelvic extension have been excluded.

Case Histories

C. M. Female child, born in February 1957, was admitted at the age of 2 weeks, oedematous with acute retention of urine. Rectal examination revealed a large cystic mass in the pelvis. At operation the tumour was densely adherent to the rectum. It was extremely soft and, when dissecting the tumour, it ruptured causing spillage of necrotic tumour into the pelvic cavity. The tumour was incompletely excised. Histologically, it was undifferentiated neuroblastoma. She was given vitamin B_{12} but no radiotherapy. Six months after operation the tumour was palpable per abdomen as well as rectally. Two months later the mass had become smaller, but 2 years following surgery the tumour could not be palpated on rectal examination. She died at the age of 3 years and 5 months of unrelieved acute intestinal obstruction due to band adhesions at the referring hospital. No residual tumour was found on gross or microscopic examination.

C. C. Female child, born in August 1954, had sacral tumour noticed at birth. Biopsy of the tumour at the age of 3 months, was first reported as Chordoma. Histological examination at the Hospital for Sick Children, London, revealed this to be undifferentiated neuroblastoma. No treatment was given. At the age of 2 years and 3 months she had a large, mobile, soft mass palpable in front of the rectum and attached to its walls. Partial excision was performed leaving half the mass *in situ*. The specimen weighed 93 gms. and consisted largely of mature ganglioneuroma but showed some residual areas of immature neuroblastoma. Vitamin B_{12} was given for 2 years. At the age of 8 years and 4 months a small nodule was palpable on the anterior surface of the sacrum, rectally, but at the age of 17 years she is free of tumour and of symptoms.

A. A. Male child, born in December 1956, was admitted to the referring hospital with acute retention of urine. He always strained on defecating. Examination revealed a left-sided pelvic mass with considerable narrowing of the lumen of the rectum. At the age of 3 months a tumour measuring 10×5×5 cms. was excised, which on histological examination was undifferentiated neuroblastoma. Radiotherapy was not given but he had a course of vitamin B_{12}. Parents moved to London when he was 6 years of age. He is now 16 years old and free of tumour.

B. C. In November 1950, a male infant, 7 months of age, was admitted with acute retention of urine. Suprapubic cystostomy drainage revealed a large, fixed presacral mass which was encircling the rectum. Biopsy through the rectal wall showed the tumour to be undifferentiated neuroblastoma. Surgical excision

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was not contemplated due to the child's poor general condition. Radiotherapy was considered, but not given. Vitamin B_{12} was administered. At the age of 11 months the tumour could not be palpated per abdomen. Rectal examination showed some infiltration in the region of the prostate. Laparotomy at the age of 22 months revealed only two retroperitoneal nodules to the left of the sacrum. He is now 22 years of age and free of tumour.

S. C. Female child, born in August 1958, was admitted at the age of 10 months with acute retention of urine due to a pelvic mass. At laparotomy, a large tumour was found rising out of the pelvis with several enlarged, fleshy lymph nodes lying along the internal iliac vein. The liver was not involved. The tumour was excised incompletely and 3 pieces of the sacrum were removed with it. Histological examination of the tumour showed it to be undifferentiated neuroblastoma. She was given radiotherapy and vitamin B_{12}. Two and a half years following surgery it was felt that she had a massive presacral recurrence but 2 years later no tumour was palpable either per abdomen or on rectal examination. Ileal loop urinary diversion was performed because of her neurogenic bladder. She is now 14 years of age and free of tumour.

G. W. In May 1963, a male child 14 months of age was admitted with a large sacral tumour. The tumour was incompletely excised on 2 occasions. The tumour was ganglioneuroblastoma. He was given vitamin B_{12} for 2 years. He was well until December 1967 when he developed a palpable lymph node in the inguinal region. Excision biopsy of the gland revealed involvement by neuroblastoma. In January 1968 further excision of the presacral tumour was performed. The iliac and inguinal lymph nodes were excised. The tumour was ganglioneuroblastoma and the lymph nodes were replaced by metastatic neuroblastoma. In February 1968, a fourth attempt at incomplete excision was undertaken because the tumour was causing bowel and bladder pressure symptoms. At the age of 10 years the child is free of symptoms. There is residual area of thickness on rectal examination.

B. L. In November 1954 a male child, one year and 11 months of age was seen with a history of the mother having noticed dilated veins and then a swelling in the region of his left buttock when he was 6-months-old. At operation, a large presacral mass was found to be continuous with the superficial lesion extending through the sacral foramina and was incompletely excised. Histological examination showed the major part of the excised tumour was composed of ganglioneuroma with areas of ganglioneuroblastoma. In 1958, because of increasing bowel and bladder symptoms, due to the bulk of the tumour, further incomplete excision of the tumour was undertaken. The coccyx was excised. Histologically, the tumour was now a well-differentiated ganglioneuroma which was actively growing and in which many of the ganglion cell were multinucleated. The child is well, but has pelvic tumour which is producing increasing pressure symptoms.

Clinical Findings

The age and sex of the children at the time of diagnosis are given in Table 1. Four of the 7 children were male. In 4 of the children, the presenting symptom was acute retention of urine and in the other 3, the tumour was palpated at birth or soon after. All the tumours could be felt on abdominal examination. The lymph nodes and the liver were not palpable in any of the children at presentation. There were no neurological symptoms or signs in any of the children. Their blood pressure was normal.

TABLE 1. *Case Summaries*

Name	Sex	Age at Diagnosis	Presentation	Operative Findings	Histology	Post-operative Follow-up	Age at Last Follow-up
C. M.	Female	2/52	acute urinary retention	1957 incomplete excision of tumour	undifferentiated neuroblastoma	spontaneous regression	Died. Pelvis free of tumour
C. C.	Female	3/12	palpable sacral mass	1954: biopsy 1956: incomplete excision of tumour	Biopsy: undifferent. neuroblastoma 1956: ganglioneuroblastoma	spontaneous maturation regression	17 years. Free of tumour
A. A.	Male	3/12	acute urinary retention	1956 incomplete excision of tumour	undifferent. neuroblastoma	spontaneous regression	16 years. Free of tumour
B. C.	Male	7/12	acute urinary retention	1950: biopsy 1952: only 2 nodules	Biopsy: undifferent. neuroblastoma	spontaneous regression	22 years. Free of tumour
S. C.	Female	10/12	acute urinary retention	1959: incomplete excision of tumour	Undifferent. neuroblastoma with lymph node spread of tumour	spontaneous regression	14 years. Free of tumour
G. W.	Male	1 2/12	1963: palpable sacral mass 1967: palpable inguinal lymph nodes	1963: 2 attempts at incomplete excision of tumour 1967: excision biopsy of lymph nodes 1968: 2 attempts at incomplete excision of presacral tumour	1963: ganglioneuroblastoma 1967: lymph node replaced by neuroblastoma 1968: ganglioneuroblastoma. Lymph nodes replaced by neuroblastoma	spontaneous maturation	10 years. Palpable presacral tumour
B. L.	Male	1 11/12	1954: palpable sacral mass 1958: bowel and bladder pressure symptoms due to tumour	1954: incomplete excision of tumour 1958: incomplete excision of tumour	1954: ganglioneuroma; few areas of ganglioneuroblastoma 1958: ganglioneuroma	spontaneous maturation	20 years. Palpable presacral tumour

Four of the children had a hypochromic anaemia but their blood pictures were otherwise normal. No abnormality was detected on bone marrow examination in the 2 children who had this test performed. Vannilyl mandelic acid estimations performed preoperatively in two children (C. M. and S. C.) were within normal limits.

Calcification in the tumour was observed in G. W. and B. L. Erosion of the sacral foramina was seen in 3 (B. L., G. W. and S. C.). Skeletal survey and chest X-rays of all the children showed no distant metastases. In all the children who had intravenous pyelography performed, dilatation of the upper urinary tract due to ureteric obstruction was demonstrated. The ureters were displaced laterally by a large intrapelvic mass. Cystogram demonstrated indentation of the bladder in two children.

Treatment

At operation, the tumours were large with big dilated veins coursing across and through the malignant tissue. In S. C., 257 gms. of tumour tissue was excised and a similar amount left behind. The liver was not involved in any of the children. Iliac lymph nodes were replaced by metastatic tumour in 2 children (S. C. and G. W.); in S. C. at the first exploration and in G. W. at the second operation performed at an interval of 4 years.

Complete excision of the tumour was not possible in any of the 7 children. In 5 more than half the tumour was left in the pelvis, and in B. C. only a biopsy was performed. The tumour tissue was often necrotic, and in C. M., a major spillage of tumour cells occurred during dissection.

In 2 children (G. W. and B. L.) the tumour was partially removed on more than one occasion. This was undertaken because it was causing pressure symptoms. B. L. had 2 and G. W. 4 attempts at incomplete excision of the tumour. In one child (B.C.) who had only a biopsy of the tumour, a second operation, 15 months later, revealed only 2 retroperitoneal nodules to the left of the sacrum.

All, except one child (B. L.), were given vitamin B_{12} for varying periods of time. Only S. C. was given radiotherapy.

Histological examination of the excised specimen showed it to be a cellular neuroblastoma with a high degree of malignancy in five children (C. M., C. C., A. A., B. C., and S. C.). In S. C., the iliac lymph nodes were replaced by neuroblastoma. In G. W. the tumour was ganglioneuroblastoma with some residual areas of immature neuroblastoma on all the 4 occasions that the tumour was excised. The inguinal and iliac lymph nodes were replaced by neuroblastoma when the tumour on both occasions was actively growing ganglioneuroma, in which many of the ganglion cells were multinucleated. Histology of the first excised specimen contained areas of ganglioneuroblastoma. In C. C. partial excision of the tumour 2 years after the primary operation showed that the tumour had matured to a ganglioneuroma with some residual areas of immature neuroblastoma.

Results

Six children are alive following treatment and they are now 22, 20, 17, 16, 14 and 10 years of age. One child died at the age of 3 years and 5 months. There is operative and histological proof of spontaneous maturation and regression of the tumour occurring in one child (C. C.). In C. M. autopsy performed at the referring hospital confirmed the clinical observation that the tumour had undergone spontaneous regression. The pelvis was free of tumour and death had occurred from intestinal obstruction, subsequent to band adhesions from previous surgery. Spontaneous regression of the tumour had occurred in two other children (B. C. and S. C.). This was confirmed at surgical re-exploration. In a fifth child (A. A.) spontaneous regression has been diagnosed on clinical grounds. In G. W. the tumour is ganglioneuroblastoma and there has been no further tumour spread 5 years after the lymph nodes which were replaced by neuroblastoma were removed. The seventh child has ganglioneuroma, although when the tumour was first excised there were some residual areas of ganglioneuroblastoma. Hence these tumours (G. W. and B. L.) have been classified as examples of spontaneous maturation of neuroblastoma. Of the 6 children alive, 2 (C. C. and B. C.) are free of tumour and of symptoms and signs. Four have neurogenic bladders and altered bowel physiology. Ileal loop urinary diversion has been performed in S. C. and it is more than likely that the remainder will require surgical intervention in the future.

Discussion

Survival in children with neuroblastoma is affected by the patients age at the time of diagnosis and radiological evidence of bone metastases, which implies a poor prognosis.[7,8,11] Another important factor is the site of origin of the primary tumour. Some reported series[9,10,12] have suggested that a better prognosis exists when the tumour originates in the neck, thorax or pelvis, than when it arises in the abdomen.

In this series all the children were under 2 years of age at the time of diagnosis, 5 of them being 10 months or younger. All the children had pelvic neuroblastoma only. There was no abdominal involvement, nor was there spread to the bones or any organs, except to the lymph nodes in 2 children. These 2 factors alone could account for the favourable prognosis encountered.

Bodian[2] described the use of Vitamin B_{12} in the treatment of neuroblastoma. The rationale was that the vitamin, an essential factor in the maturation of the haemopoietic tissue, encouraged the transformation of the embryonic tumour to adult benign tissue. He ascribed the favourable results to the use of vitamin B_{12}. He concluded that the first 18 months of life carried a better prognosis in vitamin B_{12} treated series, but found that this advantage of the younger age group was not manifest in the untreated series.

However, Coriell and MacAllister working with neuroblastoma material provided by Koop and Hernandez,[9] found that vitamin B_{12} was no more toxic for neuroblastoma than it is for HeLa cells or monkey kidney cells. They could not confirm Bodian's work and when the 2 series were comparable in size and age distribution they found that their survival rate without vitamin B_{12} was better than Bodian's with vitamin B_{12}. The present policy in this hopsital is not to prescribe vitamin B_{12} in the treatment of neuroblastoma.

Cushing and Wolbach[5] were the first to report that a malignant neuroblastoma could mature into a benign ganglioneuroma. Wittenborg[13] and Cole and Everson[4] confirmed that there is a higher incidence of spontaneous maturation and/or regression in patients with neuroblastoma in comparison with any other tumour. We have operative and histological proof of spontaneous maturation followed by spontaneous regression of undifferentiated neuroblastoma to ganglioneuroma occurring in one child. Spontaneous regression occurred in four other children, confirmation of which was obtained on surgical re-exploration in 2, autopsy examination in one and on clinical grounds in the fourth child. Of the remaining two children one has ganglioneuroblastoma with some residual areas of immature neuroblastoma and the other has ganglioneuroma.

Apart from the 2 children who are free of tumour and signs and symptoms the remainder either have a neurogenic bladder or bowel or both, consequent to the surgery or due to involvement by tumour tissue. The favourable prognosis encountered in these 7 children appears to be due to the young age at the time of diagnosis and the pelvic site of these tumours. Spontaneous maturation and/or regression has been noted to occur in sites other than abdominal neuroblastoma by other observers.

Summary and Conclusion

Seven children with pelvic neuroblastoma between the ages of 2 weeks and one year 11 months at the time of diagnosis are described. Six are alive, having undergone spontaneous maturation/regression, the seventh child died of intestinal obstruction but the pelvis was free of tumour. The better prognosis is considered to be due to the young age at the time of presentation and the site of the tumour.

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References

1. Bill, A. H., Hartmann, J. R. and Beckwith, J. B.: The Unique Biology of Childhood Tumours with Special Reference to the Biology of Neuroblastoma. Pacific Med. Surg., **75**: 281, 1967.
2. Bodian, M.: Neuroblastoma. Pediat. Clin. N. Amer., **6**:449, 1959.
3. Bodian, M.: Neuroblastoma. An Evaluation of its Natural History and the Effects of Therapy, with Particular Reference to Treatment with Massive Doses of Vitamin B_{12}. Arch. Dis. Childh., **38**:606, 1963.
4. Cole, W. H. and Everson, T. C.: Spontaneous Regression of Cancer. Philadelphia, W. B. Saunders, 88, 1963.
5. Cushing, H. and Wolbach, S. B.: The Transformation of a Malignant Paravertebral Sympathicoblastoma into a Benign Ganglioneuroma. Amer. J. Path., **3**:203, 1927.
6. Dargeon, M. W.: Tumours of Childhood. New York, Paul B. Hoeber Inc., 28, 1960.
7. De Lorimier, A. A., De Bragg, K. U. and Linden, G.: Neuroblastoma in Childhood. Amer. J. Dis. Childh., **118**: 441, 1969.
8. Gross, R. E., Farber, S. and Martin, L. W.: Neuroblastoma Sympatheticum: A Study and Report of 217 Cases. Pediatrics, **23**:1179, 1959.
9. Koop, C. E. and Hernandez, J. R.: Neuroblastoma: Experience with 100 Cases in Children. Surgery, **56**:726, 1964.
10. Miller, R. M., Tragis, D. G., Jaffe, N. and Vawter, G. F.: Favourable Outlook for Children with Mediastinal Neuroblastoma. J. Pediatr. Surg., **7**:xxx, 1972.
11. Section Survey, Surgical Section. American Academy of Paediatrics J. Pediatr. Surg., **3**:191, 1968.
12. Snyder, W. H., Hastings, T. N. and Pollock, W.: Pediatric Surgery. Chicago, Year Book Medical Publisher, 1962.
13. Wittenborg, M. H.: Roentgen Therapy in Neuroblastoma: Review of 73 Cases. Radiology, **54**:679, 1950.

Gastric Acid Secretion in Patients with a Symptomatic Gastroesophageal Reflux and Patients with Esophageal Strictures

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REFLUX OF GASTRIC ACID into the esophagus is responsible for changes of the esophageal mucosa, producing clinical symptoms and various complications.[2,3,5,8,12] The severity of the esophagitis was reported to have been correlated with the degree of gastric acidity.[6] According to this concept, patients with esophageal strictures and their lower esophagus lined with gastric epithelium (Barrett's syndrome) should have greater acid secretion when compared to control subjects and similar or greater acid secretion than patients with a symptomatic gastroesophageal reflux and hiatal hernia.

The purpose of this paper is to report the gastric acid secretion results in a prospective study in patients with strictures of the esophagus and to compare their results to those obtained in control subjects and in patients with hiatal hernias and gastroesophageal reflux.

Material and Methods

Three groups of patients were studied. All were males.

Group A. Control Subjects. Twenty-three subjects without gastrointestinal diseases served as controls. All had normal upper gastrointestinal radiographs. The mean age of this group was 49 years (range 22 to 72 years).

Group B. Hiatal Hernia Patients. Thirty-three adult patients with hiatal hernia were included in this group. They had a mean age of 48 years (range 22 to 70). All had symptoms of gastroesophageal reflux, (heartburn and/or regurgitation) with a mean duration of 5.7 years (range 2 to 12 years). In all patients a sliding hiatal hernia of more than 3 cm. in diameter was demonstrated on upper gastrointestinal series. The radiological spots were taken in the recumbent position. Radiological reflux as elicited by the water siphonage test[16] was present in 29 cases (88%) and was negative in 4. An associated duodenal ulcer was found in 3 patients. In 18 cases an esophagoscopy was performed and endoscopic evidences of esophagitis was observed. In 12 of these patients one or more biopsies were taken. Histologic evidence of esophagitis was noted in every biopsy.[18] None of the biopsies had columnar epithelium.

Group C. Patients with Esophageal Strictures. The group studied included 27 consecutive patients, each with an esophageal stricture and the lower esophagus lined with columnar epithelium. The mean age was 54 years (range 22 to 74). Twenty-five had dysphagia with a mean duration of 3.5 years. All had symptoms of gastroesophageal reflux with a mean duration of 6.3 years (range 1 to 15 years). Stricture in the mid or lower esophagus was established radiologically. All had a sliding hiatal hernia. Four cases also had an associated duodenal ulcer. The confirmation of the diagnosis was based in the simultaneous radiological and manometrical study in 19 patients as described before.[10,11] Twenty-four had endoscopic studies and biopsies were taken above and below the stricture in order to examine for the presence of columnar epithelium within the lower esophagus. Biopsies demonstrated columnar epithelium in the area of the stricture.

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TABLE 1. *Basal Acid Output* (mEq/hr.)

	N	Mean		SE	P
Normals (A)	23	3	±	0.4	A vs B ns
Hiatal hernias (B)	23	2.9	±	0.4	B vs C ns
Esophageal strictures (C)	27	4.7	±	1.2	A vs C ns

N: number of cases
SE: standard error of the mean
ns: not significant

TABLE 2. *Maximal Acid Output* (mEq/hr)

	N	Mean		SE	P
Normals (A)	23	16.4	±	1.7	A vs B ns
Hiatal hernias (B)	23	15.6	±	1.9	B vs C ns
Esophageal strictures (C)	27	18.0	±	2.8	A vs C ns

N: number of cases
SE: standard error of the cases
ns: not significant

The augmented histamine test as described previously was performed in each case.[7] All patients were fasted for 12 hours. A Levin tube No. 14 was placed in the most dependent portion of the stomach and controlled fluoroscopically. Basal acid secretion was collected in four 15 minutes samples. Thirty minutes after the beginning of the basal collection, Clorfenamine 20 to 30 mgr. was administrated subcutaneously. At the end of basal collection histamine acid phosphate 40 μg/kg. was injected and gastric secretion was collected in four 15 minute samples. Volume was measured and acid concentration was determine by pH determination of the sample and using Moore's table of conversion.[7]

The results of basal acid output (BAO) and maximal acid output after histamine (MAO) are expressed in mEq/hr. All values on results are mentioned as mean plus minus standard error of the mean (SE). Student's t test for unpaired values was used in statistical analysis of the data.[21]

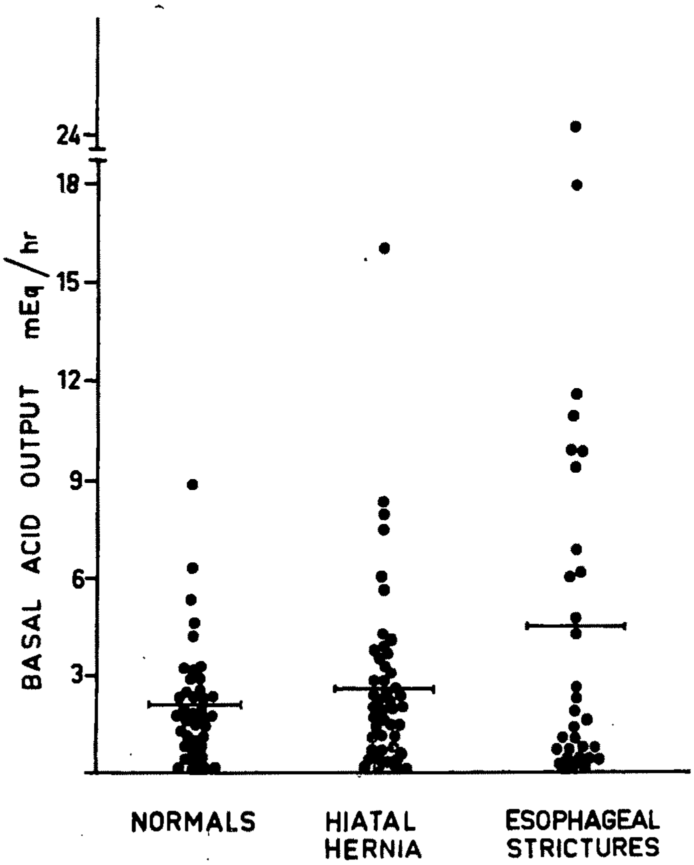

FIG. 1. Basal acid output in control subjects and patients with symptomatic hiatal hernia and patients with esophageal strictures. Horizontal lines represent the mean output of each group.

Results

No significant differences in age or duration of the reflux symptoms were observed in hiatal hernia patients compared to the cases with esophageal strictures ($p > 0.2$).

Basal Acid Secretion.

The results of the basal gastric acid secretion are shown in Table 1. Although a greater mean basal output was obtained in the group of patients with esophageal strictures (Group C), this was not significantly different from the control group (Group A) ($p > 0.1$) or from hiatal hernia patients (Group B) ($p > 0.1$).

The individual values of each group are shown in Fig. 1.

Histamine Stimulated Secretion:

After histamine no significant differences were obtained in output among the 3 groups ($p > 0.1$) (Table 2). Individual values are shown in Fig. 2.

Among the 4 patients with esophageal strictures and an associated duodenal ulcer, 3 had markedly increased basal acid output.

The 3 patients with hiatal hernia and duodenal ulcer had the highest basal acid output among their group.

No correlation was found among basal acid output and any type of mucosa lining the lower esophagus.

Discussion

In this study we could not confirm previous reports that have suggested an association between a sliding hiatal hernia and hypersecretion of gastric acid.[2,3,5,8,12] Also, a close correlation has been reported to exist among size of the hernia and amounts on acid secreted.[4] Our results confirm previous findings that in patients with symptomatic hiatal hernia there was no significant increase in acid secretion compared with normal subjects.[1,20,23] The only circumstance when a high acid output was found in hiatal hernia patients occurred in those who have an associated duodenal ulcer.[1,19,23] In addi-

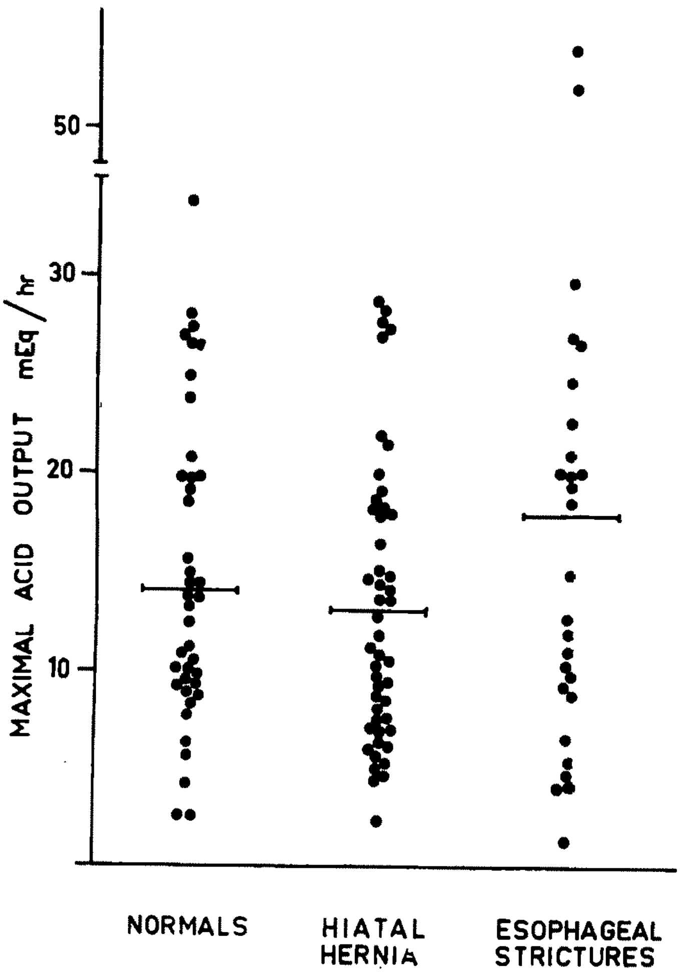

FIG. 2. Gastric acid output after "maximal" histamine stimulation in normal subjects and patients with hiatal hernia and esophageal strictures. Horizontal lines represent the mean output of each group.

tion, patients who represent the final stage of the gastroesophageal reflux, such as stricture of the esophagus secondary to acid reflux with hiatal hernia, do not have higher acidity than normal subjects or patients with hiatal hernia.

In a small minority of the cases of esophageal strictures, high values of basal output were observed. In some of them an associated duodenal ulcer was also noted. In some, a Zollinger Ellison syndrome may be suspected. However, a positive correlation has been reported between elevated basal serum gastrin and resting gastroesophageal sphincter pressure in patients with Zollinger Ellison syndrome.[14] Careful manometric studies in all these patients with esophageal strictures showed hypotensive or normotensive gastroesophageal sphincter pressure (Larrain, Csendes and Uribe unpublished data).

Giles, *et al.*[9] and Ward[22] have reported that perfusion of the lower esophagus with acid increased basal gastric acid output in normal subjects and in patients with hiatal hernia. When there was an associated esophagitis, this stimulation was more pronounced and they postulate a vicious cycle that could be established and worsen the existing inflammation. According to this theory, patients with strictures of the esophagus should have higher acid secretion than normal subjects. This however, was not observed in our patients.

Since patients with a simple gastroesophageal reflux (Group B) and with strictures of the esophagus (Group C) have similar features in acid secretion, and since no relationship was seen between the lining mucosa and acid values of basal secretion, these data suggest that a congenital heterotopia of columnar mucosa could explain mainly the etiology of the strictures of the esophagus with columnar epithelium. In association to this heterotopia, the presence of reflux in the adult life could precipitate the appearance of symptoms and complications.

The use of surgical procedures to reduce acid secretion in patients with strictures of the esophagus should only be indicated in those cases with associated duodenal ulcer and or hypersecretion. The majority, if operated, can be approached with conservative surgical repairs such as the posterior gastropexy.[13,15]

Summary

Gastric acid secretion was studied in normal subjects, in patients with hiatal hernia and gastroesophageal reflux and in patients with esophageal strictures. No significant differences in basal acid output or after histamine stimulation were observed between the 3 groups ($p > 1$).

No significant differences in age, or duration of gastroesophageal reflux symptoms could be established ($p > 0.1$).

These data suggest that a congenital ectopic gastric mucosa may be the major defect in the pathogenesis of the benign strictures of the esophagus.

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References

1. Beauconsfield, P.: Reflux Esophagitis; Its Diagnosis and Treatment. Gastroenterology, 24:369, 1953.
2. Casten, D. F.: Esophageal Hernia and Gastric Secretion. Arch. Surg., 88:255, 1964.
3. Casten, D. F.: Peptic Esophagitis Hiatal Hernia and Duodenal Ulcer. Am. J. Surg., 113:638, 1967.
4. Casten, D. F., Bernhang, A., Nach, R. J. and Spinjia, J.: A Physiological Basis for the Surgical Treatment of Sliding Esophageal Hiatal Hernia. Surg. Gyn. Obstet., 117:87, 1963.
5. Castro, L., de P.: Reflux Esophagitis as the Cause of Heartburn in Pregnancy. Am. J. Obstet. Gynec. 98:1, 1967.

6. Cocco, A. E. and Brantigan, O. C.: Esophagitis: Diagnosis and Surgical Treatment. Am. Surg., **169**:857, 1969.
7. Csendes, A., Orrego, H. and Heitmann, P.: Características de la secreción gástrica en enfermos con úlcera duodenal. Rev. Médica de Chile, **96**:788, 1968.
8. Flood, C. A., Wells, J. and Baker, D.: Esophageal Reflux in Simple Heartburn. Gastroenterology, **28**:28, 1955.
9. Giles, G. R., Clark, C. G. and Buchan, R.: Effect of Esophageal Perfusion with Acid on Basal Gastric Secretion. Gut, **9**:52, 1968.
10. Heitmann, P., Strauszer, T., Sapunar, J. and Larrain, A.: Lower Esophagus Lined with Columnar Epithelium Morphological and Physiological. Considerations. Gastroent., **53**:611-623, 1967.
11. Heitmann, P., Csendes, A. and Strauzer, T.: Esophageal Strictures and Lower Esophagus Lined with Columnar Epithelium. Am. J. Dig. Dis., **16**:307, 1971.
12. Herrington, J. L.: The Treatment of Esophageal Hiatal Hernia. Arch. Surg., **89**:379, 1962.
13. Hill, L. D. and Talios J. A.: An Effective Operation for Hiatal Hernia: An Eight Year Approximal. Ann. Surg., **166**:681, 1967.
14. Isenberg, J., Csendes, A. and Walsh, J.: Resting and Pentagastrin Stimulated Gastroesophageal Sphincter Pressure in Patients with Zollinger Ellison syndrome. Gastroenterology, **61**:655, 1971.
15. Larrain, A.: Technical Considerations in Posterior Gastropexy. Surg. Gynec. Obstet., **132**:299, 1971.
16. Linsman, J.: Gastroesophageal Reflux Elicited While Water (Water Siphonage Test) Its Clinical Correlation with Pyrosis. Am. J. Roentgenol., **94**:325, 1965.
17. Moore, E. W. and Scarlata, R. W.: The Determination of Gastric Acidity by the Glass Electrode. Gastroenterology, **49**:178, 1965.
18. Palmer, E. D.: Subacute Erosive Peptic Esphagitis Histopathological Studies. Arch. Pathol., **59**:51, 1955.
19. Pridie, R. B.: Incidence and Coincidence of Hiatus Hernia. Gut, **7**:188, 1966.
20. Silber, W.: Augmented Histamine Test in the Treatment of Symptomatic Hiatal Hernia. Gut, **10**:611, 1969.
21. Snedecor, G. W. and Cochran, W. G.: Statistical Methods. Ames. Iowa State University Press, 1967.
22. Ward, A. S.: A Esophageal Reflux and Gastrin Secretion. Gut, **11**:738, 1970.
23. Williams, C. B., Lawrie, J. H. and Follest, A. P. M.: Acid Secretion in Symptomatic Sliding Hiatus Hernia. Lancet, **1**:182, 1967.

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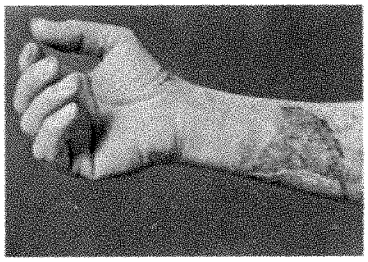

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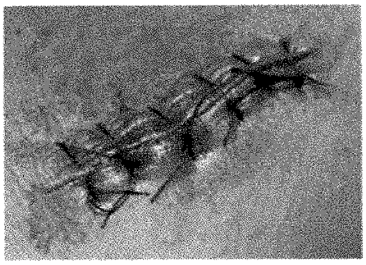

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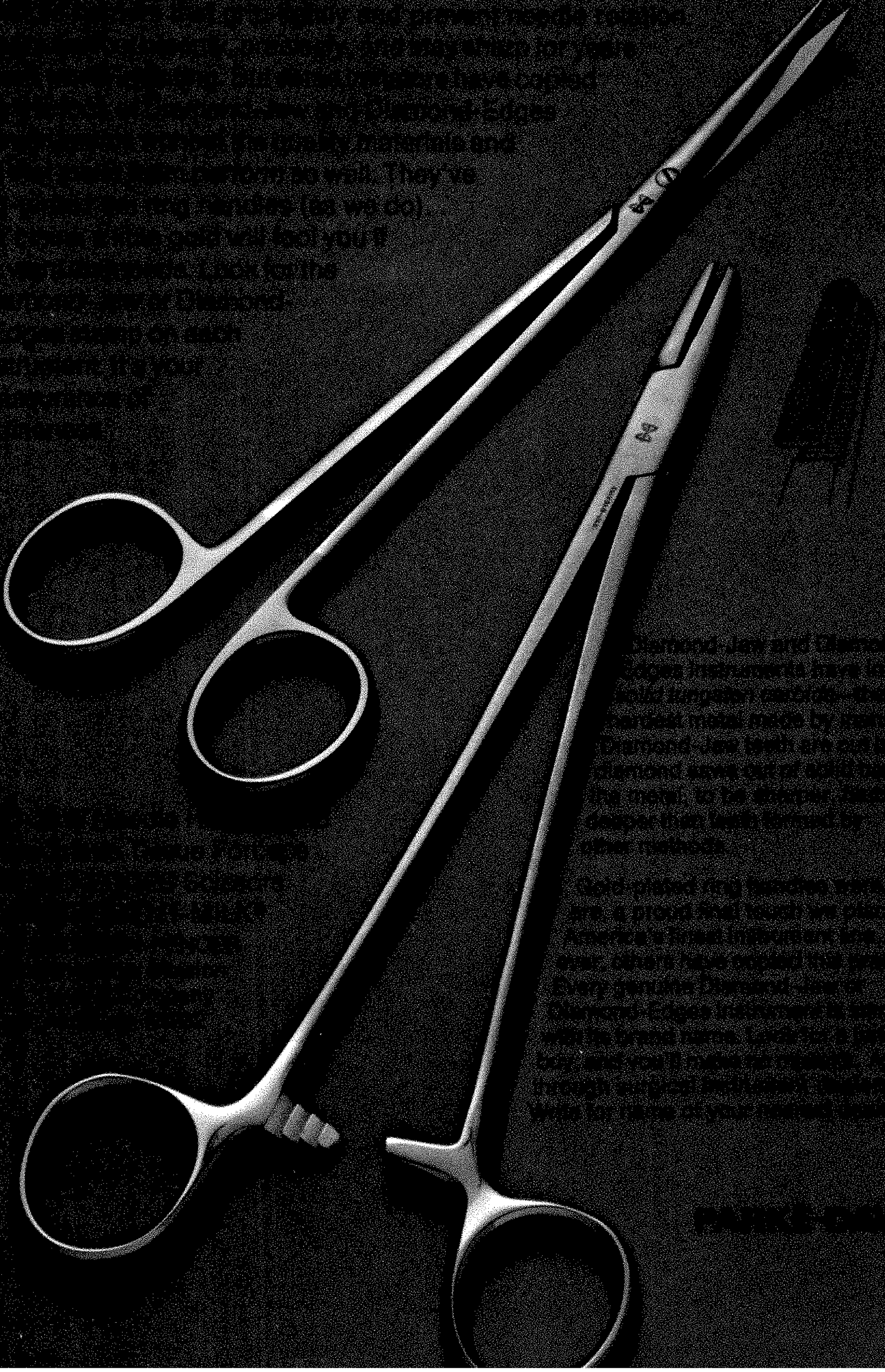

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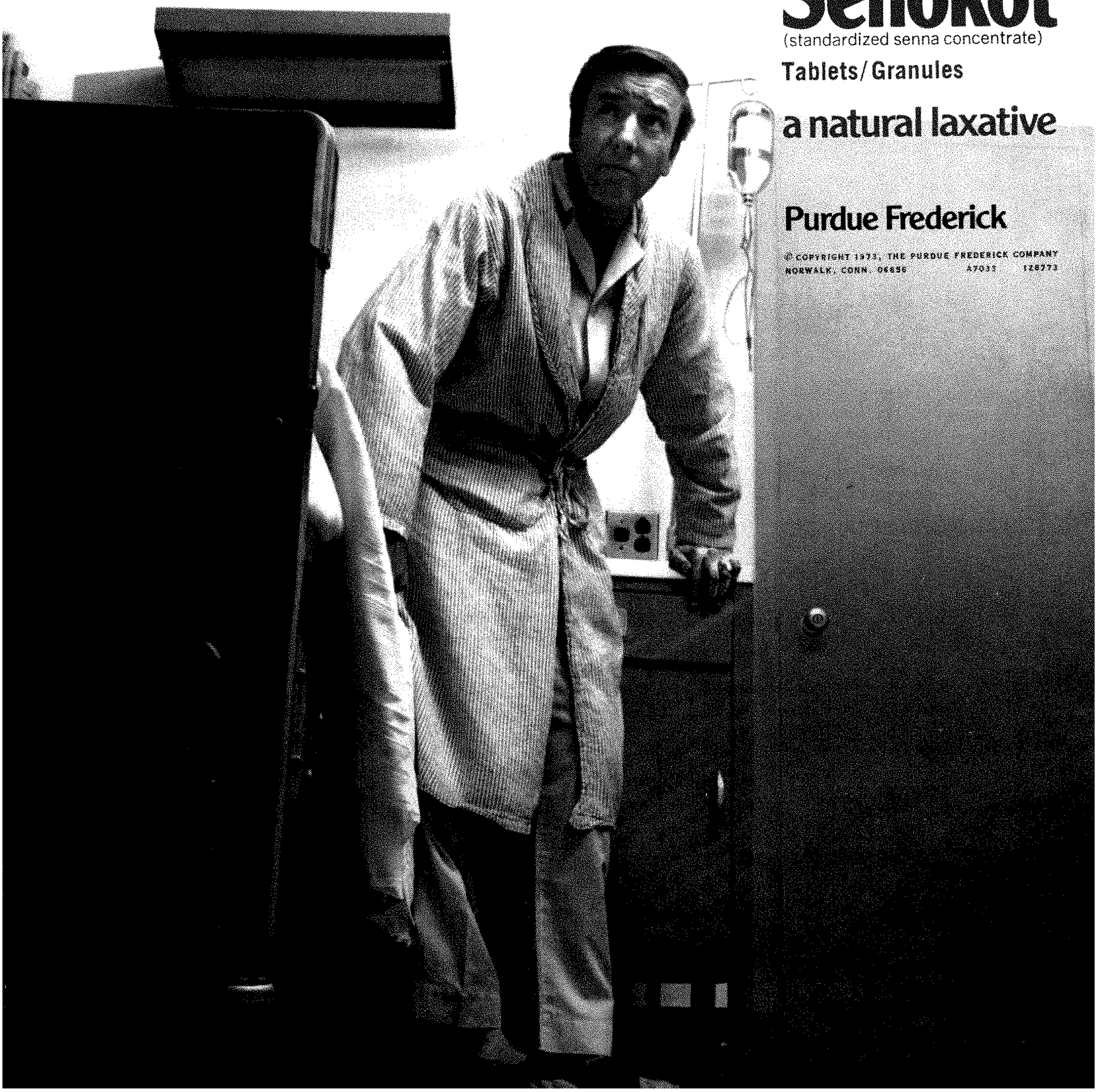

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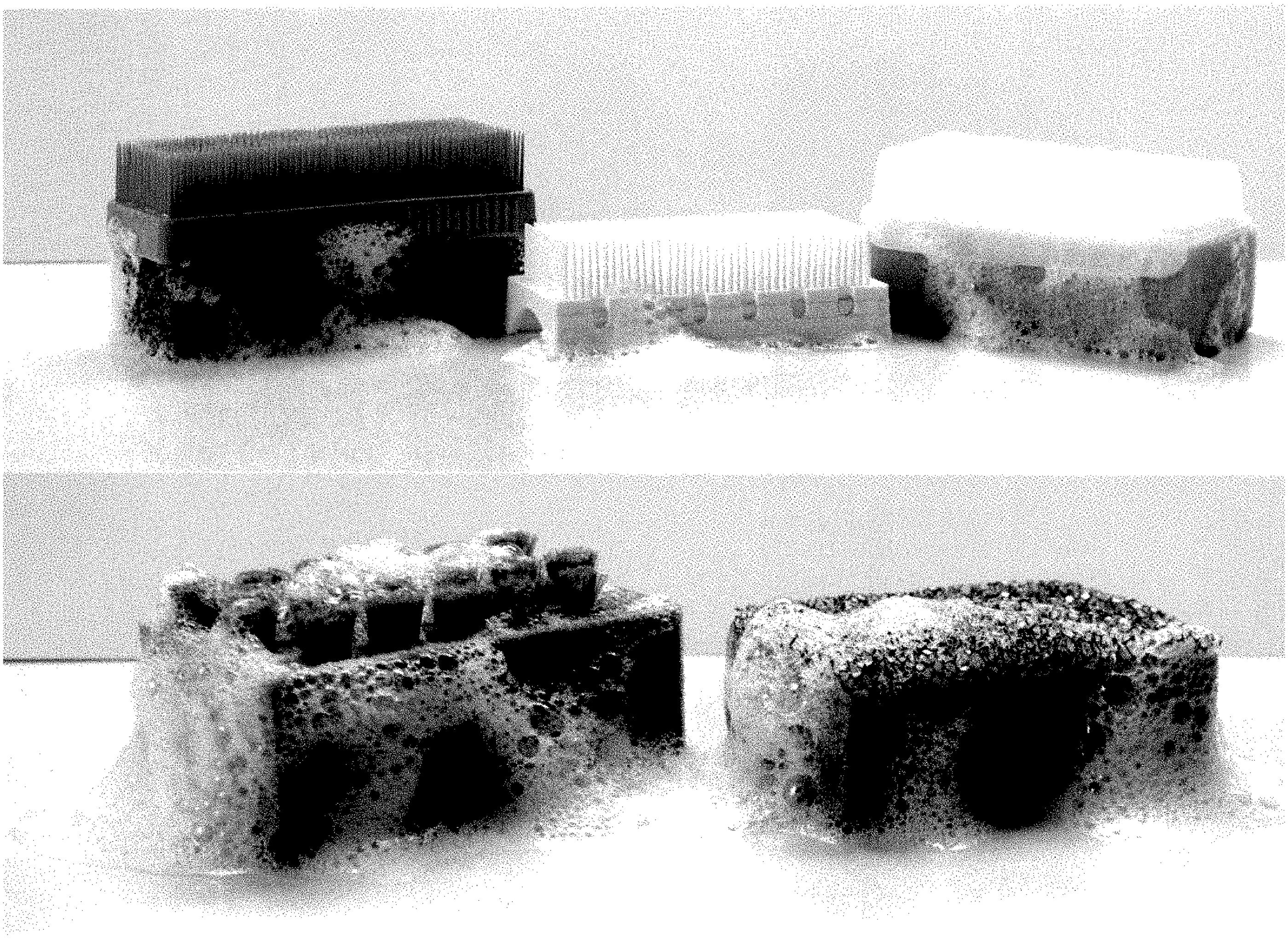

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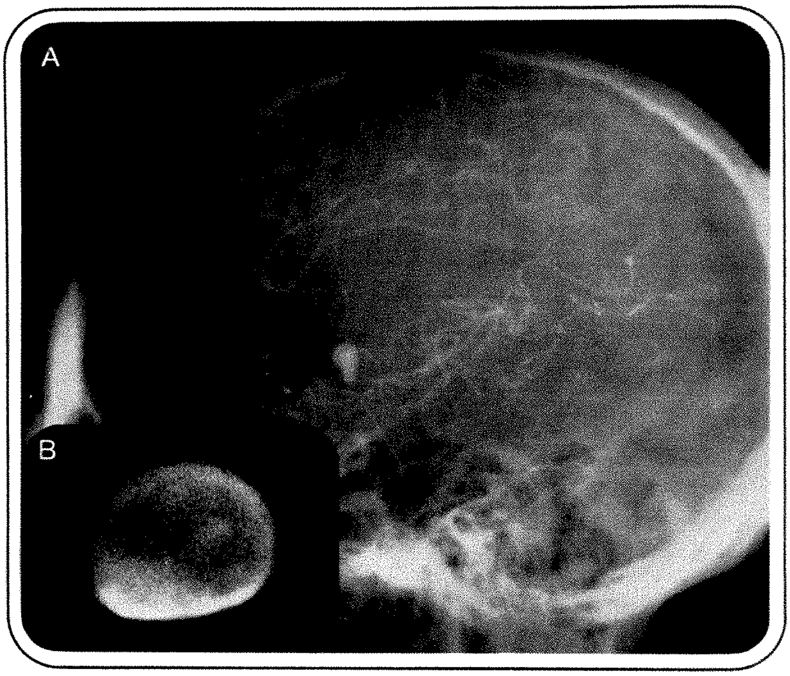

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Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control.

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components.

It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: Rinse thoroughly after use, especially from sensitive areas such as the scrotum and perineum.

If left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms. Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions.

pHisoHex should be discontinued promptly if signs or symptoms of cerebral irritability occur. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin or exposure to a powder accidentally containing approximately 6.5% hexachlorophene. Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only.* If swallowed, pHisoHex is harmful especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precautions: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, and in plastic bottles of 1 gallon.

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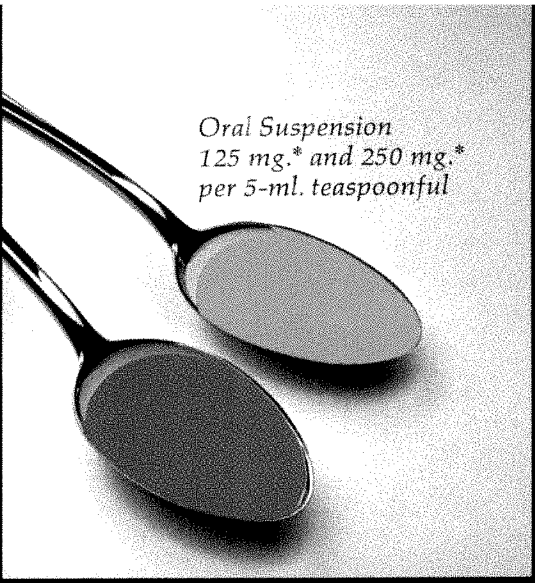

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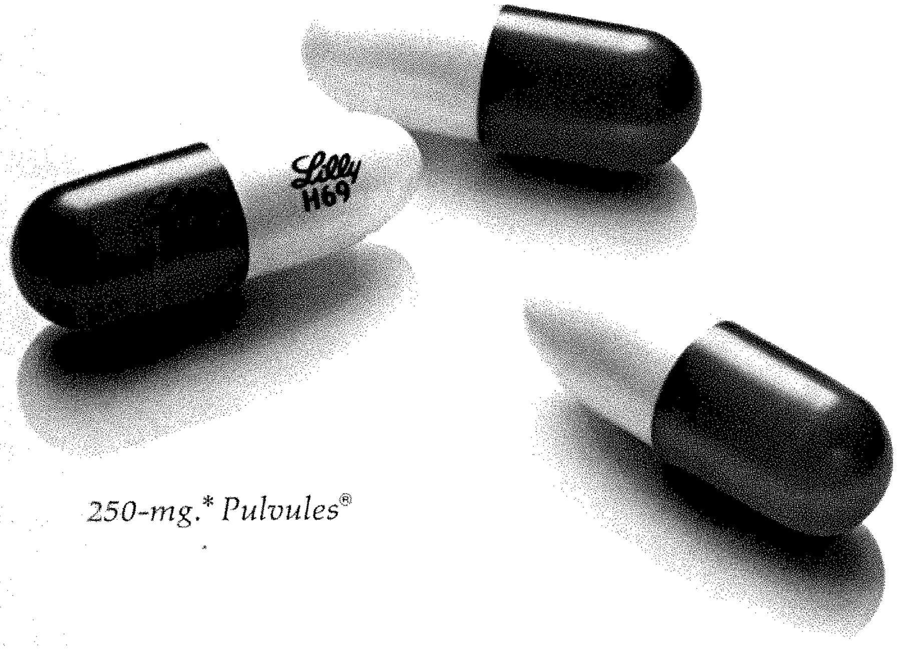

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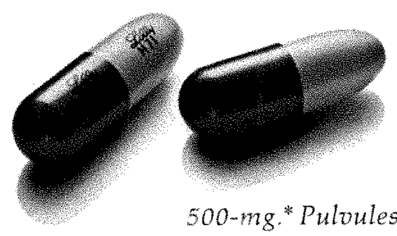

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ANNALS OF SURGERY

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Endotracheal Damage During Continuous Ventilatory Support

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GRADUAL APPRECIATION of the value of continuous support in the treatment of respiratory failure has increased its use. However, tracheal damage from prolonged intubation is proving to be a real problem for those who use this mode of therapy.[1,7,9,11,13,16,17,19,20,22] Our own experience is similar to that of the increasing number of reports of tracheal damage.[6] We have seen substantial tracheal erosions (often as early as 48 hours after intubation), tracheal dilatation, esophageal fistulae and erosions into the carotid vessels in our ventilated patients. Most of the damage occurs at the site of the occluding cuff. The pressure exerted on the trachael wall by the inflated cuff is generally recognized as the primary cause of the tracheal damage.[5–7,16,21]

To reduce or prevent the damage the composition and design of the occluding cuff has been changed to reduce the pressures exerted on the tracheal wall.[2,3,8,10,12,14–16] We have monitored the tracheal damage endoscopically for the past 2 years. During that time, we have observed the effects of a variety of cuffs available commercially and newly developed cuffs designed to reduce the damage. The purpose of this report is to document our experiences with these cuffs so that their advantages and disadvantages can be appreciated.

Materials and Methods

Our patients requiring continuous ventilatory support with a tracheostomy tube in the medical and surgical intensive care units were studied. Every other day the tracheostomy cuff pressure was measured with a mercury manometer, the cuff deflated, the tube removed, the trachea examined through the tracheostomy stoma with a 5 mm Olympus flexible fiberoptic bronchoscope and photographed, a new tube inserted and the cuff inflated to a measured minimal pressure which could occlude the tracheal lumen to allow effective ventilation. The tubes were changed only if the general condition of the patients permitted; apneic patients had their cuff pressures measured only. The patients in the medical intensive care unit had their cuffs deflated every 1–2 hours for suctioning and reinflated by the nursing staff. The patients in the surgical intensive care unit had their cuffs undisturbed after the cuff pressure measurements until the time for the next tube change (usually 48 hours). The choice of ventilators was determined by the clinical condition of the patient. The 6 cuffs studied are depicted in Fig. 1. The first 3 represent standard commercially available tubes used for ventilating our patients at the onset of the study; the Portex tubes were used in a majority of the patients. The last 3 tubes have high-volume, low-pressure bulky cuffs recently developed in an attempt to occlude the tracheal lumen at lower cuff pressures so as to prevent pressure necrosis.

Sixty patients were studied from 12 hours to 66 days: the study periods averaged 11 days. These 60 patients

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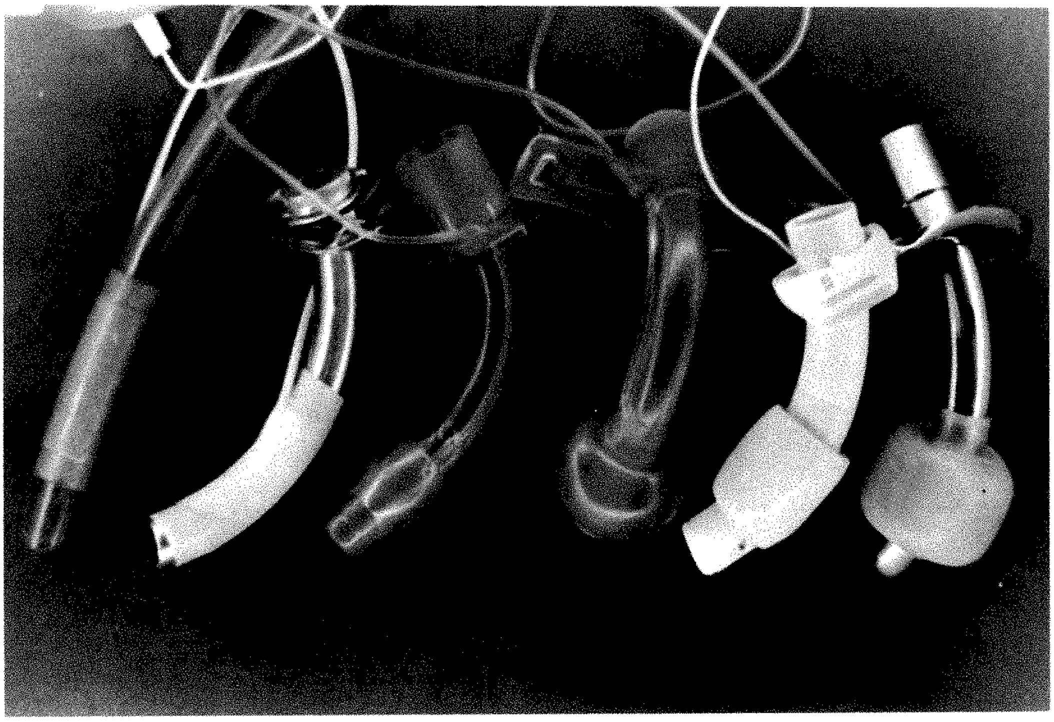


Fig. 1. The cuffs studied. Left to right: Rusch endotracheal tube with latex rubber cuff; Jackson tracheostomy tube with latex rubber cuff; Portex tube with polyvinyl-chloride cuff; Portex tube with polyvinyl-chloride cuff hyperinflated with hot water; Shiley tube with polyvinyl-chloride cuff, and Pilling tracheostomy tube with Foregger latex rubber Soft-Cuf™. The latter three cuffs represent the new high-volume, low-pressure cuffs. Each cuff was inflated with 10 cc's of air, allowed to equalize to atmospheric pressure and clamped.

developed severe respiratory insufficiency requiring continuous ventilatory support as a complication of a variety of primary illnesses. Table 1 is a summary of the general categories of their primary illnesses. The largest group of patients were those who had undergone abdominal surgery (23 patients). Eighteen stuporous or comatose medical patients formed the bulk of those ventilated in the medical intensive care unit; these patients had cerebral vascular accidents, meningitis, renal failure, liver failure or drug overdosage as their primary disease. Fewer numbers were ventilated for thoracic surgical indications (7 patients) or traumatic injuries (6 patients).

Results

Fig. 2 is a scattergram of the cuff pressures measured in our patients. The conventional cuffs all required high pressures. The Rusch endotracheal tube averaged 120 mm Hg, the cuffed Jackson 174 mm Hg and the Portex 136 mm Hg. The newer cuffs required considerably less pressure. The modified Portex averaged 23 mm Hg, the Shiley 46 mm Hg, and the Soft-Cuf™ pressures were the lowest at 18 mm Hg. In a few instances the modified Portex and Soft-Cuf™ were bulky enough to achieve satisfactory ventilation at atmospheric pressure. The size of the newer cuffs expanded at atmospheric pressure is illustrated in Fig. 1.

The cuffs of the conventional tracheostomy tubes caused tracheal erosions seen in *all* cases at the first examination 48–72 hours after tracheostomy had been performed. The eroded areas were easily recognized and were generally found at the junction between the membranous and cartilaginous walls of the trachea (Fig. 3a).

Table 1. *Primary Illness of Patients Requiring Continuous Ventilatory Support*

Abdominal surgery	23
Thoracic surgery	7
Trauma	6
Coma of medical etiology	18
Cardiogenic shock	4
Chronic respiratory disease	2
Total patients	60

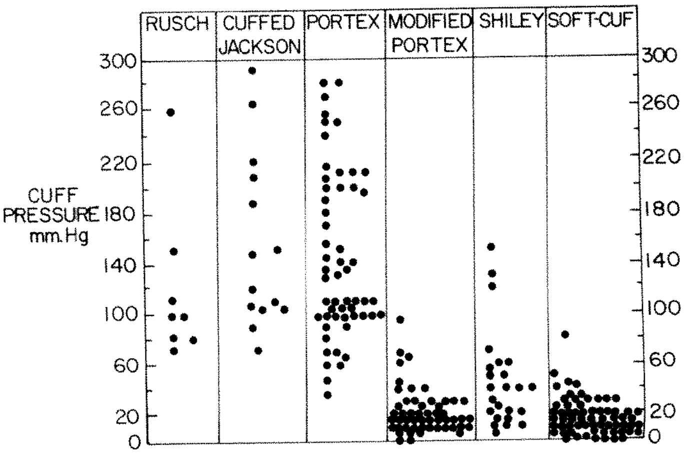


Fig. 2. Cuff pressures measured in patients receiving continuous ventilatory support.

The tracheal erosions persisted and progressed as long as continuous ventilation was required (Fig. 3b). There was regression of the erosions only after continuous ventilation was discontinued and the cuff was inflated only for intermittent positive pressure breathing therapy (Fig. 3c). Persistent continuous support in some instances resulted in perforation of the trachea (Fig. 9). Endotracheal tube intubation also damaged the trachea (Fig. 4).

The high-volume, low-pressure modified Portex and Soft-Cuf™ cuffs also showed damage as early as 48 hours, but to a lesser degree. In many instances the damage was so minimal that it was not fully appreciated at the time of the bedside examination of the trachea with the fiberoptic bronchoscope but careful examination of the Ektachrome color transparency slides showed that there were areas of erosions present at 48 hours. The Soft-Cuf™ cuffs produced the least damage (Figs. 5a and 5b). The level of the intracuff pressure influenced the damage. When an unnecessarily high cuff pressure of 40 mm Hg was measured just prior to changing of the tube significant damage was seen in one patient using the Soft-Cuf™ (Fig. 6). Careful reinflation of the cuff required only 18 mm Hg pressure for effective occlusion and ventilation. A similar experience occurred with a modified Portex (Figs. 7 and 10).

The Shiley low pressure cuffs required higher cuff pressures than the other two high volume cuffs and produced damage that was easily recognized with the bronchoscope. Cuff pressures higher than 100 mm Hg were required in one of the 5 patients in which we used it; on the 10th day, we observed a perforation into the esophagus of that patient (Fig. 8). In this patient and another patient we had difficulty aspirating air from the inflated cuff in some instances and could do so only after inflating with excess air. We discontinued its use after having used the cuff in 5 patients.

We experienced 3 instances of acute obstruction with our early model of the Soft-Cuf™ secondary to prolapse

Fig. 3a.

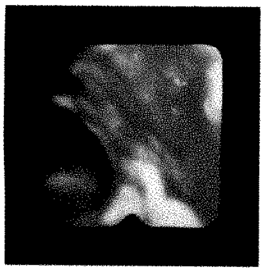


Fig. 3b.

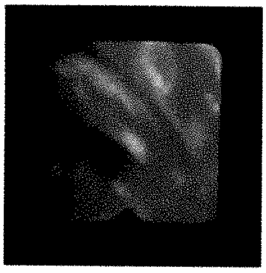


Fig. 3c.

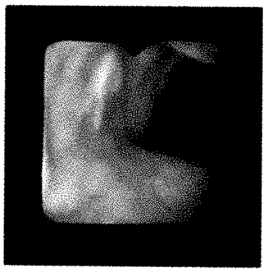


Fig. 4.

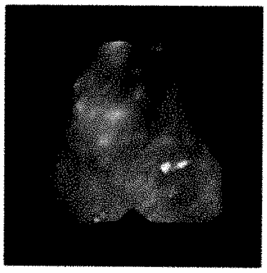
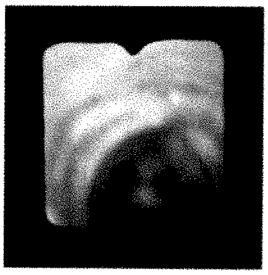


Fig. 5a.



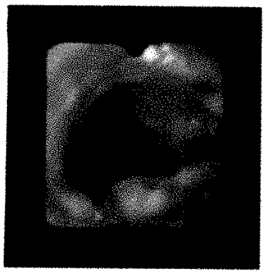


Fig. 5b.

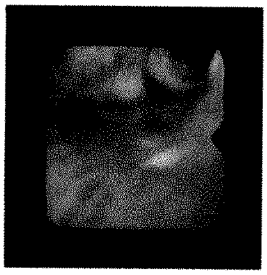


Fig. 6.

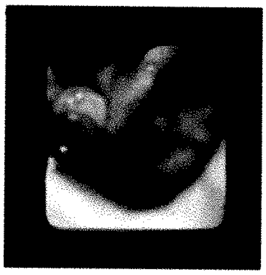


Fig. 7.

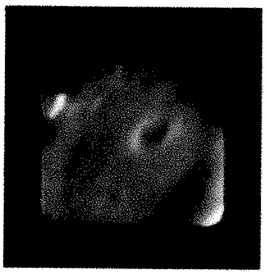


Fig. 8.

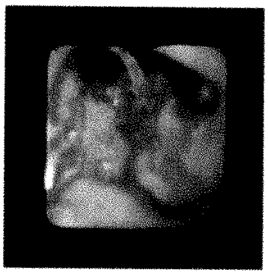


Fig. 9.

Bronchoscopic view of tracheostomy cuff damage areas. Fig. 3a. The damage seen in a patient after 48 hours of continuous ventilation via a Portex tracheostomy tube. The hemorrhagic areas seen in the right half of the color plate between islands of normal mucosa and mucous secretion represent the tracheal erosions generally seen at the junction between the membranous and cartilaginous walls of the trachea. Fig. 3b. The progression of the tracheal damage in the same patient as Fig. 3a after 10 days. Fig. 3c. Regression of the erosions seen in Fig. 3b. without deformity by the 22nd day after continuous ventilation was discontinued on the 10th day and the cuff was only inflated intermittently for intermittent positive pressure breathing therapy. Fig. 4. Tracheal damage seen after 6 days of ventilation with an endotracheal tube. Fig. 5a. Minimal tracheal erosion seen in a patient after 3 days of ventilation with a Soft-Cuf™ tracheostomy tube noted on the left wall of the trachea in the left lower quadrant. Fig. 5b. Tracheal erosion in the cartilaginous roof (between 11 and 12 o'clock) after 10 days of use in the patient illustrated in Figure 5a. The junction between the cartilaginous and membranous wall are free of erosions. Fig. 6. The severest damage seen with use of the Soft-Cuf™. The two most prominent red areas of erosions are seen in the lower right hand corner near the membranous-cartilaginous junction and at 9 o'clock along the membranous portion of the trachea. An unnecessarily high cuff pressure of 40 mm Hg was measured just prior to this photograph on the 8th day after tracheostomy; careful inflation of the cuff revealed that only 18 mmHg pressure was required for effective occlusion and ventilation. Fig. 7. Severe tracheal erosion after 21 days use of a modified Portex and a cuff pressure measurement of 95 mm Hg prior to examination; measurement 1 week previously, showed that only 15 mm Hg was required. Fig. 8. Perforation into the esophagus seen after 10 days of ventilation with a Shiley low pressure cuff in which cuff pressures higher than 100 mmHg were required. Fig. 9. A perforation into the esophagus after 24 days of use of a Portex tube. A strand of mucous (12 o'clock) is being drawn into the tracheal lumen by the airstream flowing through the fistula in the lower right quadrant with the patient's inspiratory effort. This fistula was the largest seen.

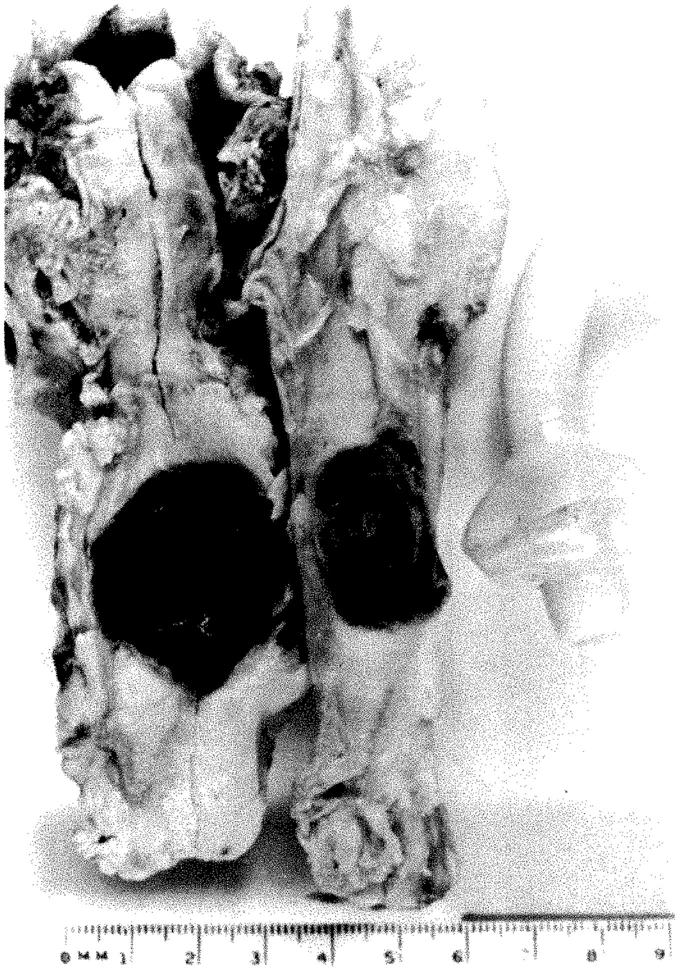


FIG. 10. Autopsy specimen of the trachea and esophagus of a patient who died 23 days after ventilation with a modified Portex. There was severe tracheal erosion and a fistula into the esophagus. Cuff pressure was measured at 95 mm Hg 2 days previously, although only 15 mm Hg pressure was found to be necessary for effective ventilation, 9 days previously.

of the inflated cuff over the distal end of the tube. The cuffs on the later tubes were moved further from the distal end to avoid this problem. There were two instances of obstruction with a Shiley tube among the thirteen used.

Discussion

This study was prompted by the high incidence of tracheal damage we saw in our ventilated patients. Our pathologists found severe damage in all autopsies performed on 54 ventilated patients previous to the study. Six different cuffs have been studied, including 3 which represented the recent trend in design change of cuffs to lower the pressure which the cuff exerts against the tracheal wall. The degree of tracheal damage seen varied from superficial erosion to perforation into the esophagus. The most severe and the most persistent damage occurred with the conventional cuffs. It appeared that the decreased pressure made possible by the bulky cuffs minimized or prevented the damage particularly if the pressure was kept below 25 mm Hg. However, there were two instances of serious damage with the bulky cuffs. In both instances excessive pressures were measured in the tube. Previous work in our laboratory has shown that most of the pressure measured in these new cuffs is also being exerted directly against the tracheal wall.[6,18]

The results of this study confirm the previous observations of others implicating pressure necrosis as the cause of the tracheal damage secondary to cuffed tracheal intubation. Although many of the newer cuffs caused minimal damage, severe damage was found when excessive pressures were used for inflation or the cuff did not occlude at pressures less than 25 mm Hg. It is therefore essential that the intracuff pressure be measured every time the cuff is inflated.

The pressure used to inflate the cuff can be easily measured at the bedside using the wall mercury manometer available at the bedside of each patient in intensive care units. Expensive electrical monitoring equipment is not necessary. The tip fits the inflating tubing without additional connections. In our surgical intensive care unit the pressure is measured each time the cuff is inflated and recorded. We try to keep the cuff pressure below 25 mm Hg.

We have noticed no significant difference in the degree of damage of tracheal erosions whether the cuffs were deflated for short periods at one or two-hour intervals or were generally left undisturbed between tube changes every 48 hours. Only when longer periods of deflation were possible and the cuff was inflated only for intermittent possitive pressure treatments did erosions regress. The amount of time that the cuffs were deflated at regular intervals was not sufficient to be of benefit. There was danger in deflating the cuffs frequently because the nursing staff periodically reinflated with excessive air when they reinflated the cuffs without measurement of the cuff pressures. In many instances the cuffs were found to have higher pressures than were measured at the previous tube changes. We feel that this was the basis of the serious complications we experienced with the bulky tubes. Some workers have avoided the pressure by using a volume controlled ventilator and limiting the expansion of the cuff so that some leak occurs with the pressure phase.[4] In practice we have found the sound produced disturbing to the nursing staff who then proceed to correct it. Such a leak produces a drying effect on the mucosa and is difficult to duplicate with each reinflation.

Summary

A series of commercially available tracheostomy cuffs including the newer bulky cuffs intended to prevent damage to the trachea have been studied in the clinical situation in order to relate the characteristics of these cuffs to the degree of tracheal damage. All cuffs studied caused damage varying from superficial erosion to tracheal perforations in the tracheas of patients requiring continuous ventilatory support. No matter which type of cuff was used, significant damage was found unless the cuff could occlude at pressures less than 25 mm Hg intracuff pressure. The new bulky cuffs could do this but the pressure had to be monitored with each inflation to avoid excessive unnecessary pressure.

References

1. Andrews, M. J. and Pearson, F. G.: Incidence and Pathogenesis of Tracheal Injury Following Cuffed Tube Tracheostomy with Assisted Ventilation. Ann. Surg., **173**:249, 1971.
2. Arens, J. F., Ochsner, J. L. and Gee, G.: Volume-limited Intermittent Cuff Inflation for Long-term Respiratory Assistance. J. Thorac. Cardiovasc. Surg., **58**:837, 1969.
3. Auchincloss, J. H., Jr., Gilbert, R. and Mullison, E.: A New Self-inflating Tracheostomy Cuff of Silicone Rubber for Use in Patients Requiring Mechanical Aid to Ventilation. Amer. Rev. Resp. Dis., **97**:706, 1968.
4. Bryant, L. R., Trinkle, J. K. and Dubilier, L.: Reappraisal of Tracheal Injury from Cuffed Tracheostomy Tube Experiments in Dogs. JAMA, **215**:625, 1971.
5. Carroll, R., Hedden, M. and Safar, P.: Intratracheal Cuffs: Performance Characteristics. Anesthesiology, **31**:275, 1969.
6. Ching, N. P., Ayres, S. M., Paegle, R. P., Linden, J. M. and Nealon, T. F., Jr.: The Contribution of Cuff Volume and Pressure in Tracheostomy Tube Damage. J. Thorac. Cardiovasc. Surg., **62**:402, 1971.
7. Cooper, J. D. and Grillo, H. C.: The Evolution of Tracheal Injury due to Ventilatory Assistances Through Cuffed Tubes. Ann. Surg., **169**:334, 1969.
8. Cooper, J. D. and Grillo, H. C.: Experimental Production and Prevention of Injury due to Cuffed Tracheal Tubes. Surg. Gynec. Obstet., **139**:1235, 1969.
9. Fishman, N. H., Dedo, H. H., Hamilton, W. K., Hinchcliffe, W. A. and Roe, B. B.: Postintubation Tracheal Stenosis. Ann. Thorac. Surg., **8**:47, 1969.
10. Geffin, B. and Pontopiddan, H.: Reduction of Tracheal Damage by the Prestretching of Inflatable Cuffs. Anesthesiology, **31**:462, 1969.
11. Geffin, B., Grillo, H. C., Cooper, J. D. and Pontopiddan, H.: Stenosis Following Tracheostomy for Respiratory Care. JAMA, **216**:1984, 1971.
12. Grillo, H. C., Cooper, J. D., Geffin, B. and Pontopiddan, H.: A Low-pressure Cuff for Tracheostomy Tubes to Minimize Tracheal Injury. J. Thorac. Cardiovasc. Surg., **62**:898, 1971.
13. Hedden, M. D. Ersoz, C. J. and Safar, P.: Tracheoesophageal Fistulas Following Prolonged Artificial Ventilation *via* Cuffed Tracheostomy Tubes. Anesthesiology, **31**:281, 1969.
14. Kamen, J. M. and Wilkinson, C. J.: A New Low-pressure Cuff for Endotracheal Tubes. Anesthesiology, **34**:482, 1971.
15. McGinnis, G. E., Shively, J. G. and Magovern, G. J.: Controlled Pressure Occluding Cuffs for Endotracheal Tubes. Abstr. 16.7. Twenty-third Annual Conference on Engineering in Medicine and Biology, Washington, D. C., November 1970.
16. Miller, D. R. and Sethi, G.: Tracheal Stenosis Following Prolonged Cuffed Intubation: Cause and Prevention. Ann. Surg., **171**:283, 1970.
17. Murphy, D. A., MacLean, L. D. and Dobell, A. R. C.: Tracheal Stenosis as a Complication of Tracheostomy. Ann. Thorac. Surg., **2**:44, 1966.
18. Nealon, T. F., Jr. and Ching, N.: Pressures of Tracheostomy Cuffs in Ventilated Patients. N. Y. State J. Med., **71**:1923, 1971.
19. Pearson, F. G. and Andrews, M. J.: Detection and Management of Tracheal Stenosis Following Cuffed Tube Tracheostomy. Ann. Thorac. Surg., **12**:359, 1971.
20. Pearson, F. G., Goldberg, M. and Da Silva, A. J.: Tracheal Stenosis Complicating Tracheostomy with Cuffed Tubes. Arch. Surg., **97**:380, 1968.
21. Shelly, W. M., Dawson, R. B. and May, I. A.: Cuffed Tubes as a Cause of Tracheal Stenosis. J. Thorac Cardiovasc. Surg., **57**:623, 1969.
22. Törnvall, S. S., Jackson, K. H. and Oyanedel, E. T.: Tracheal Rupture, Complication of Cuffed Endotracheal Tube. Chest, **59**:237, 1971.

Hemangiopericytoma

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JOHN W. PICKREN, M.D.

HEMANGIOPERICYTOMA has been described as a variant of angiosarcoma (hemangioendothelioma) with relatively benign biological aggressiveness. It can develop anywhere there are capillaries; hence, it causes many unique problems of diagnosis and therapy. The tumor may develop over a period of months and even years and in patients of all ages. The most critical aspect of treatment is an accurate histological diagnosis separating it from other angiosarcomas and benign tumors of blood vessels such as the solitary glomus tumor.

This report reviews our experience with 13 cases of hemangiopericytomas treated at Roswell Park Memorial Institute.

Clinical Features and Manifestations

Hemangiosarcomas may occur at any age and equally in men and women. In this group of 9 females and 4 males, the age at the time of diagnosis ranged from 24 years to 73 years; 8 occurred between the age of 30–60.

The tumor may develop wherever capillaries are present. There are published reports of hemangiopericytomas occurring in the thoracic cavity,[5,14] head and neck area,[8,16,25,27,36] genitourinary tract,[4,12,37,38] peritoneal cavity,[11,18,32] retroperitoneum,[9] the soft tissues of trunk and extremities,[30,42,44] and the thoracic spine.[13] In this series, the majority of the tumors were located in the extremities and retroperitoneal tissues (Table 1).

Clinically, the hemangiopericytomas usually present as a *painless* enlarging mass as was true in 10 of our 13 patients. In contrast, its possible counterpart, the *benign* glomus tumor, of which the *solitary* group is the most common type, is usually located on an extremity and characteristically presents as a *small painful* mass. Table 2 lists helpful features in the differentiation of the benign solitary glomus tumor from the hemangiopericytomas.

The duration of the hemangiosarcomas, before definitive therapy, varied from a maximum of 10 years to a minimum of 2 weeks. Measurements of the primary tumor at the time of diagnosis was documented in 11 cases; the smallest tumor was 1 × 1 cm. and the largest was 25 × 23 cm. and weighed 1,800 grams as illustrated in Fig. 1. The average diameter of the tumors was 8–9 cm. This illustrates dramatically the lack of pain associated with these tumors. The slow growth of the tumor rarely results in ulceration or hemorrhage that would prompt an earlier search for care.

In this series of patients, there were no unusual metabolic manifestations of the tumor. There are published reports of the tumor presenting as: hypoglycemia,[7] hypoglycemia and masculinization in a female,[19] as hypertension and hypokalemia on a renin basis,[10,23,35] and possibly hypertension and congestive failure on an A-V shunt basis.[17] Angiographic studies may be helpful in delineating the size, extent and infiltration of the tumor,[2,9,17,21] but there is no substitute for a histological diagnosis.

Treatment and Results

A clinical resume of each patient including the various kinds of treatment are listed in Table 3. Four patients (Case Nos. 4, 5, 6, 10) were treated by local surgical excision and of these, the first recurrence was *local* in 2 patients within a period of 4 months; and in the other 2, the first recurrence was at a distant site after 7 years and 3 months, respectively. In those patients (Case Nos. 1, 2, 3, 11)whose tumors were removed by a local excision followed by a wide excision, the first recurrence

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was at the local site in one patient at 2 years and at a distant site in another patient in 2 years.

Patients No. 7, 8, and 9 are of particular interest in that radiation therapy appeared beneficial. Radiation therapy provided a 40% reduction of the tumor mass in patient 7, thus converting a nonresectable lesion into a resectable lesion. Patient 8 had one distant pulmonary metastasis at the time of the initial diagnosis and radiation therapy produced a 30% reduction in the fixed primary tumor mass, thus converting the primary lesion into a resectable lesion. This was followed by thoracotomy and wedge resection of the pulmonary metastasis. In patient 9, residual tumor was present at the lines of resection. This incomplete initial excision was followed by postoperative radiation and this may have delayed local recurrence for 7 years.

The remaining 2 patients treated with radiation include patient 12 who died in the postoperative period and patient 13 who had an unusual primary site in the lumbar vertebrae. His follow-up period is short, but radiation therapy relieved the pain and he has returned to part-time employment.

The gross appearance of the tumor could be evaluated from clinical notes or personal observation in 10 of the 13 cases. A striking feature was "encapsulation." This characteristic is misleading since, as noted above, the tumors may be locally invasive.

Seven, or about 50%, of these tumors must be classified as malignant in that there were confirmed distant metastasis. Three, or about 30%, of the patients died from extensive local or metastatic growths less than 5 years from the time of diagnosis. Other patients died of their disease after 5, 10 and 11 years. Two patients are living with disease; the longest survival is 10 years, 8 months. Four patients are living free of disease from 4 years, 7 months to a maximum of 12 years, 10 months.

TABLE 1. *Anatomic Distribution of Hemangiopericytoma in this Series*

Site	No. of Cases
Extremities	5
Retroperitoneal	3
Head and Neck	1
Anterior Chest Wall	1
Trunk	1
Spine L_5	1
Bladder	1

Discussion

Hemangiopericytoma is a relatively uncommon tumor. In 1969, Backwinkel[3] collected 224 cases from the literature which had had adequate follow-up. This entity was introduced by Stout and Murray[41] in 1942 to distinguish this puzzling tumor of blood vessel origin from a closely related benign lesion, the glomus tumor and from other kinds of angiosarcomas. The hemangiopericytoma is composed of proliferating capillaries and spindle-shaped cells resembling the pericytes of Zimmerman.[45] Stout[39] considered pericytes to be the principal cell type in both tumors. The origin, structure, and function of pericytes is a controversial subject. These cells are normally present around capillaries and considered to be a specific type of cell closely related to smooth muscle cells, but without contractile fibers.

Benign glomus tumors may occur wherever arteriovenous anastomosis are present. Glomus cell development occurs in the postnatal period and disarrangements in this process may result in a range of lesions with various degrees of vascular and cellular components. The glomus tumors were divided by Hueston[20] into three clinical categories: 1) solitary glomus tumors, 2) multiple painful glomus tumors, and 3) multiple painless glomus tumors. The majority of all glomus tumors are solitary with

TABLE 2. *Differential Features of Solitary Glomus vs. Hemangiopericytoma Tumor*

	Solitary Glomus	Hemangiopericytoma
Pain	Usually severe paroxysmal	Usually absent
Size	Small (1–5 mm.)	Varies—usually large
Anatomical Location	Skin, subcutaneous tissues hands, feet & often of nail beds (less common viscera)	All anatomical sites of body
Vascular Element	Arterial side vascular system	Capillary or venous side vascular system
Malignant Potential	Absent	Approximately 50%
Light Microscopy	Polyhedral cells c̄ large round or ovoid nuclei & clear cytoplasm	Sheets of ovoid or spindle cells c̄ indistinct cytoplasm & large various size nuclei
	Tumor cells separated by hyalinized eosinophilic stroma	Tumor cells around small vascular spaces
	No mitosis	Mitosis may be seen
Electronmicroscopy	Two cells: polyhedral smooth muscle cell & mast cells c̄ granules	Cells of various shapes and sizes with no basement membrane
	Large cytoplasm with a number of filaments	These cells separated by basement membrane of endothelial cells
	Mitochondria are round or ovoid	Mitochondria rod-shaped or ovoid

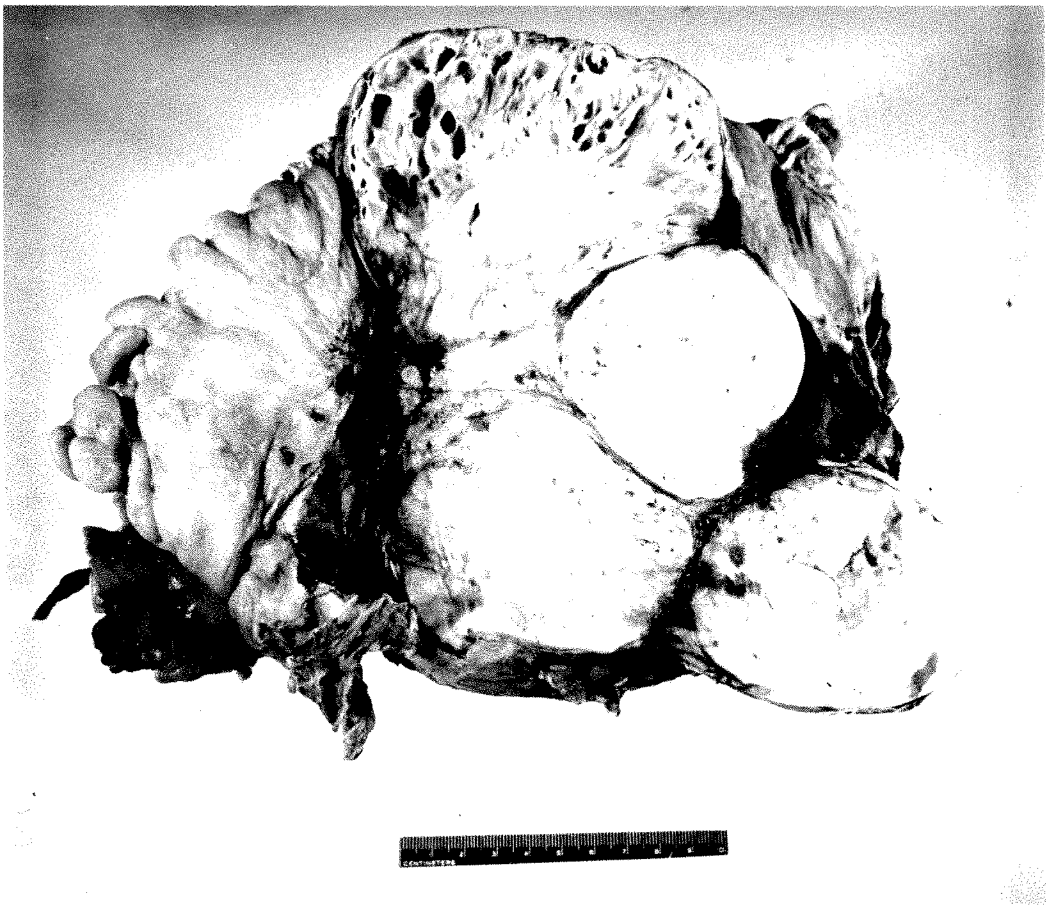

FIG. 1. Resected hemangiopericytoma of the retroperitoneal area with attachment to the sigmoid colon. Illustrates the growth in size prior to producing symptoms. This patient had only constipation of three months and vague pain of only one month duration.

predilection for the extremities and subungal sites. They are usually less than 5 mm in diameter[28] and characteristically present with severe paroxysmal pain triggered by touch or change in temperature. The multiple painful glomus tumors have identical histologic features, primarily cellular and are usually localized to a circumscribed area of the body. The solitary and multiple painful glomus tumors (some classify as hamartomas) may occur in deeper tissue structures including the viscera.[1,30,34] The multiple painless group may be widely distributed with dozens of lesions and their histological apearance is more vascular.

Electron microscopy studies[24,29,43] may be helpful in differentiating the hemangiopericytomas and glomus tumors.

Hemangiopericytoma is a slow growing, but malignant tumor with a capacity for local invasion and spread through the bloodstream. There is no single histologic criterion which will reliably differentiate the malignant from the benign hemangiopericytoma.[10] In this group of 13 patients, 54% were classified as malignant because of metastasis during their clinical course.

This tumor, like other soft tissue sarcomas, is difficult to control at their primary site by limited local excision. Like the cells of other sarcomas, they may divide to form long files of tumor cells along muscle and nerve sheaths, blood vessel compartments, and fascial septa. Unfortunately, there are no published reports on the incidence of local recurrence following local excision. Wide surgical excision of all lesions is the treatment of choice and in those areas in which the underlying anatomical structures do not permit an adequate excision, more radical procedures must be considered. The anatomical site of the lesion is the important factor in therapy. If the lesion is adjacent to a joint or over the tibia or on the foot, conservative therapy would be proximal amputation. Lesser procedures must be considered more radical and entail more risk when one considers the biological nature of the tumor. Case 4 in this series illustrates this point. This 65-year-old white female presented with a painless mass in the lateral aspect of the knee. Local excision was performed. Two years later, a local recurrence was noted and again local excision performed. During the next 2 years, she developed 3 local recurrences which were treated by local excision. By the end of the third year, pulmonary metastases were noted. She died 5 years, 2 months from the time of diagnosis. This patient *may* have had a longer survival or cure if a

TABLE 3. *Clinical Resume of 13 Patients with Soft-tissue Hemangiopericytoma*

Case No.	Age Sex	Pain	Site—Duration Size Cm.		Treatment	"Pseudo-capsule"	1st Recur., Site Duration, Treatment	Other Recurrences & Treatment	Survival
1	34F	No	Mid-thigh 3 × 3	−1 yr.	[1]L.E.—[2]W.E.	Yes			Living NED* 8 yrs.
2	63M	No	Elbow 1 × 1	−1 yr.	Wide L.E.	Yes			Living NED 6 yrs 4 mo.
3	24F	No	Upper thigh 18 × 18	−9 mo.	L.E.—hemipelvectomy	Yes	Distant lung 27 mo. Wedge exc.		Living NED 12 yrs 10 mo
4	65F	No	Lower thigh 2 × 4	−1 mo.	L.E.	Yes	Local 6 mo., W.E.	Local x4 in 2 yrs. L.E. x4 distant lung 3 yrs.	Died Disease 5 yr 2 mo
5	50F	No	Upper thigh 6 × 7	−6 mo.	L.E.	Yes	Distant 7 yr. Laminectomy	Multiple bones, R.T. pain relief	Died Disease 9 yr 5 mo
6	59F	No	[3]R.p. 12 × 12	−2 mo.	L.E.	Yes	Local 4 mo., R.T. 5000	Local 10 yrs., T.R. 3000 50%	Living Disease 10 yrs 8 mo
7	39M	Yes	R.p. 25 × 23	−3 mo.	[4]Bx., [5]R.T. 3500 40% size, W.E. in 1 yr.	Yes			Living NED 4 yr 7 mo
8	56M	Yes	R.p. + lung 25 × 15	−3 mo.	Bx., R.T. 2600 to Primary 30%. W.E. primary, wedge ex. lung	Yes		Left lung	Died Disease 2 yr 9 mo
9	51F	No	Parotid gland 12 × 10	−5 yr.	Incomplete exc. post-op, R.T. 1200	Yes	Local 7 yrs.—2 yrs. partial exc. R.T. 4000	Lung 2 yrs.	Died Disease 11 yr 5 mo
10	39F	No	Back 4 × 4	−3 mo.	L.E.	—	Distant 3 mo., L.E.	Lung, groin, ribs Rx.—R.T.	Died Disease 2 yr 3 mo
11	37F	No	Chest wall 3 × 3	−5 mo.	L.E.—radical mastectomy	Yes	Local 2 yrs., L.E.	Liver 5 mo.	Died Disease 2 yr 5 mo
12	73F	No	Bladder	−2 wks.	Ex., 6 mo. later W.E.	—			Died Post-op
13	62M	Yes	L_5 Spine	−10 yrs.	Bx., R.T. 6000	—			Living

[1] L.E.—local excision
[2] W.E.—wide excision
[3] R.p.—retroperitoneum
[4]Bx.—biopsy
[5]R.T.—radiation in rads
*NED—no evidence of disease

supracondylar amputation had been performed initially.

Case 3 provided a second illustration of the desirability of a more radical surgical resection of the primary lesion. This 24-year-old white female presented with a large painless mass in the upper thigh buttock area. The initial procedure was a local excision. The tissue diagnosis was interpreted as malignant hemangiopericytoma. Seven days later, a hemipelvectomy was performed. She has had no further recurrence in the operative site. A wedge excision of a metastatic lesion in the lung was performed 2 years later. She has remained free of further disease, performing all functions of a housewife for her husband and children for more than 10 years.

The usefulness of irradiation therapy in the management of this neoplasm is not well defined. Published reports of its use are few and this may be due to a general consensus that most soft tissue sarcomas are radioresistant. There are reports[15,21] that this neoplasm is radioresistant, and other reports[15,22,26] suggesting relatively long term objective responses after radiation therapy. Friedman and Egan[15] suggest a tumoricidal radiation dose probably lies in the range of 7,500 to 9,000 rads administered by supravoltage or gamma-beam teletherapy over a 60 day period. They have found that lesser degrees of palliation can be achieved with smaller increments. In this small series, radiation therapy converted a nonresectable lesion to a resectable one in two instances and provided appreciable palliation in 4 other patients.

In our small series of patients, invasion of the regional lymph nodes was not confirmed in those 3 patients undergoing procedures which provided specimens for histologic study. It would seem that prophalactic excision of the regional nodes is unnecessary unless the primary lesion is in juxtoposition to them.

We have had no experience with chemotherapy of this tumor. Again, published reports are few. Bredt[6] reported a temporary objective response in one patient by administration of a combination of Vincristine and Actinomycin D. In this same patient, other agents including cyclophosphamide, methotrexate, 5-flurouracil and imidazole were ineffective. Effective control of metastatic bone disease in a child by administering various combinations of actinomycin D, cyclophosphamide, vincristine and methotrexate was reported by Ortega.[33] In the few other reported cases, actinomycin D, cyclophosphamide, nitrogen mustard and mitomycin C gave no objective response.

Summary

Thirteen cases of hemangiopericytoma treated at Roswell Park Memorial Institute are presented. The tumor was malignant in 50% of the patients as confirmed by distant metastasis. Survival is based on a lifetime clinical course rather than a five-year period because this tumor may grow slowly and recurrences may still develop after a long interval. A high recurrence rate results when simple enucleation or excision is performed on the basis that the tumor appears to be encapsulated.

Wide excision which may include amputation in selected cases is the treatment of choice. Metastatic lesions, particularly in the lung, should be evaluated and resected whenever feasible. Radiation therapy may convert a nonresectable lesion into a resectable one and provide significant palliation.

Reference

1. Appelman, H. D. and Helwig, E. B.: Glomus Tumors of the Stomach. Cancer, **23**:203, 1969.
2. Ayella, R. J.: Hemangiopericytoma, A Case Report with Arteriographic Findings. J. Radiol., **97**:611, 1970.
3. Backwinkel, K. D. and Diddams, J. A.: Hemangiopericytoma, Report of a Case and Comprehensive Review of the Literature. Cancer, **25**:896, 1970.
4. Baglio, C. M. and Crowson, C. N.: Hemangiopericytoma of Urachus; Report of a Case. J. Urol., **91**:660, 1964.
5. Blenkinsopp, W. K. and Hobb, J. T.: Pedunculated Hemangiopericytoma Attached to the Thoracic Aorta. 1966. **21**:193, Thorax.
6. Bredt, A. B. and Serpick, A. A.: Metastatic Hemangiopericytoma Treatment with Vincristine and Actinomycin D. Cancer, **24**:266, 1969.
7. Crocker, D. W. and Veith, F. J.: Mesodermal Tumors Associated with Hypoglycemia: Review of Literature and Report of a Case. Ann. Surg., **161**:418, 1965.
8. Das, A. K. and Gans, B. J.: Hemangiopericytoma of Oral Cavity: Review of Literature and Report of a Case. J. Oral Surg., **23**:456, 1965.
9. Douglas, J. L., Mitchell, R. and Short, D. W.: Retroperitoneal Hemangiopericytoma. Br. J. Surg., **53**:31, 1966.
10. Eddy, R. L. and Sanchez, S. A.: Renin-secreting Renal Neoplasm and Hypertension with Hypokolemia. Ann. Intern. Med., **75**:725, 1971.
11. Ernst, C. B., Abell, M. R. and Kahn, D. R.: Malignant Hemangiopericytoma of the Stomach. Surgery, **58**:351, 1965.
12. Farrow, G. M., Harrison, E. G., Jr., Utz, D. C. and Remine, W. H.: Sarcomas and Sarcomatoid and Mixed Malignant Tumors of the Kidney in Adults, Part I. Cancer, **22**:545, 1968.
13. Fathie, K.: Hemagiopericytoma of the Thoracic Spine. J. Neurosurg., **32**:371, 1970.
14. Feldman, F. and Seaman, W. B.: Primary Thoracic Hemangiopericytoma. Radiology, **82**:998, 1964.
15. Friedman, M. and Egan, J. W.: Irradiation of Hemangiopericytoma of Stout. Radiology, **74**:721, 1960.
16. Fuste, F. J.: Primary Hemangiopericytoma of the Orbit. J. Tenn. Med. Assn., **61**:1003, 1968.
17. Gerstmann, K. E. and Nimberg, G. A.: Hemangiopericytoma with Angiographic Studies. A Case Report. Clin. Orthop., **68**:108, 1970.
18. Goldberger, R. E. and Schein, C. J.: Hemangiopericytoma of the Omentum. Report of a Case with a Unique Presentation and Review of the Literature. Am. Surg., **34**:291, 1968.
19. Howard, J. W. and Davis, P. L.: Retroperitoneal Hemangiopericytoma Associated with Hypoglycemia and Masculinization. Del. Med. J., **31**:29, 1959.
20. Hueston, J. T.: Multiple Painless Glomus Tumors. Br. Med. J., **1**:1210, 1961.
21. Joffe, N.: Hemangiopericytoma: Angiographic Findings. Br. J. Radiol., **33**:614, 1960.
22. Kent, K. H.: Hemangiopericytoma: Report of a Case with Special Reference to Roentgen Therapy. Am. J. Roentgenol. Radium Ther. Nucl. Med., **77**:347, 1957.
23. Kihara, I., Kitamura, S., Hoshino, T., Seida, H. and Wanabe, T.: A hitherto Unreported Vascular Tumor of the Kidney: A Proposal of "Juxtaglomerular Cell Tumor." Acta Path. Jap., **18**:197, 1968.
24. Kuhn, C. and Rosai, J.: Tumors Arising from Pericytes. Ultrastructure and Organ Culture of a Case. Arch. Path., **88**: 653, 1969.
25. Lenczyk, J. M.: Nasal Hemangiopericytoma. Arch. Otolaryngal., **87**:536, 1968.
26. Mujahed, Z., Vasilas, A. and Evans, J. A.: Hemangiopericytoma: A Report of Four Cases with a Review of the Literature. Am. J. Roentgenol. Radium Ther. Nucl. Med., **82**: 658, 1959.
27. Muller, J. and Mealey, J., Jr.: Hemangiopericytoma versus Angioblastic Meningioma. A Tissue Culture Study. J. Neuropath. Exp. Neurol., **26**:140, 1967.
28. Mullis, W. F., Rosato, F. E., Rosato, E. F., Butler, C. J. and Mayer, L. J.: The Glomus Tumor. Surg., Gyn. & Obstet., **135**:705, 1972.
29. Murad, T. M., von Haam, E. and Murthy, M. S. N.: Ultrastructure of a Hemangiopericytoma and a Glomus Tumor. Cancer, **22**:1239, 1968.
30. Murray, M. R. and Stout, A. P.: Glomus Tumor; Investigation of its Distribution and Behavior, and the Identity of its "Epithelioid" Cell. Am. J. Path., **18**:183, 1942.
31. O'Brien, P. and Brasfield, R. D.: Hemangiopericytoma. Cancer, **18**:249, 1965.
32. Olsen, E. G. J. and Wellwood, J. M.: Haemangiopericytoma of the Small Intestine. Br. J. Surg., **57**:66, 1970.
33. Ortega, J. A., Finklestein, J. Z., Isaacs, H., Jr., Hittle, R. and Hastings, N.: Chemotherapy of Malignant Hemangiopericytoma of Childhood. Report of a Case and Review of the Literature. Cancer, **27**:730, 1971.
34. Riveros, M. and Pack, G. T.: The Glomus Tumor. Report of Twenty Cases. Ann. Surg., **133**: 394, 1951.
35. Robertson, P. W., Klidjian, A., Harding, L. K. and Walters, G.: Hypertension Due to a Renin-secreting Renal Tumour. Am. J. Med., **43**:963, 1967.
36. Shklar, G. and Meyer, I.: Vascular Tumors of the Mouth and Jaws. Oral Surg., **19**:335, 1965.
37. Simon, R. and Greene, R. C.: Perirenal Hemangiopericytoma. A Case Associated with Hypoglycaemia. J.A.M.A., **189**:155, 1964.
38. Spiro, R. H., Brockuier, A. and Brumschwig, A.: Pelvic Hemangiopericytoma: Review of the Literature and Report of a Case Treated by Posterior Exenteration. Obstet. Gynec., **24**:402, 1964.
39. Stout, A. P.: Tumors Featuring Pericytes: Glomus Tumor and Hemangiopericytoma. Lab. Invest., **5**:217, 1956.
40. Stout, A. P. and Lattes, R.: Tumors of the Soft Tissue. *In* Atlas of Tumor Pathology, Series 2, Fasc. I., Washington, D. C., Armed Forces Institute of Pathology, 1967.
41. Stout, A. P. and Murray, M. R.: Hemangiopericytoma; Vascular Tumor Featuring Zimmerman's Pericytes. Ann. Surg., **116**:26, 1942.
42. Tulenko, J. F.: Congential Hemangiopericytoma; Case Report. Plast. Reconstr. Surg., **41**:276, 1968.
43. Venkatachalam, M. A. and Greally, J. G.: Fine Structure of Glomus Tumor: Similarity of Glomus Cells to Smooth Muscle. Cancer, **23**:1176, 1969.
44. Vidrine, A., Jr. and Welsh, R. A.: Hemangiopericytoma; Five Cases. Surgery, **56**:912, 1964.
45. Zimmerman, K. W.: Der feiner bau der blutcapillaren. Z. Anat. Entwicklungsgesch, **68**:29, 1923.

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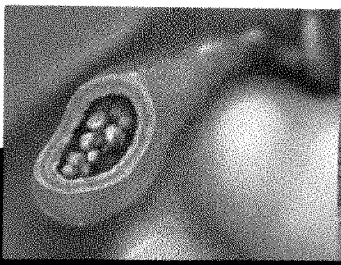

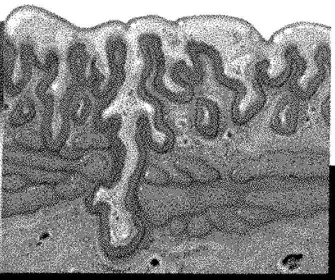

1. Artist's conception of cutaway view of gallbladder containing stones which, by causing irritation of the organ's interior wall and restricting biliary flow, may play a role in the repeated episodes of inflammation and infection associated with chronic cholecystitis.
2. Artist's conception of microscopic section of gallbladder wall showing chronic state with superimposition of inflammation, edema and necrosis due to an acute episode.

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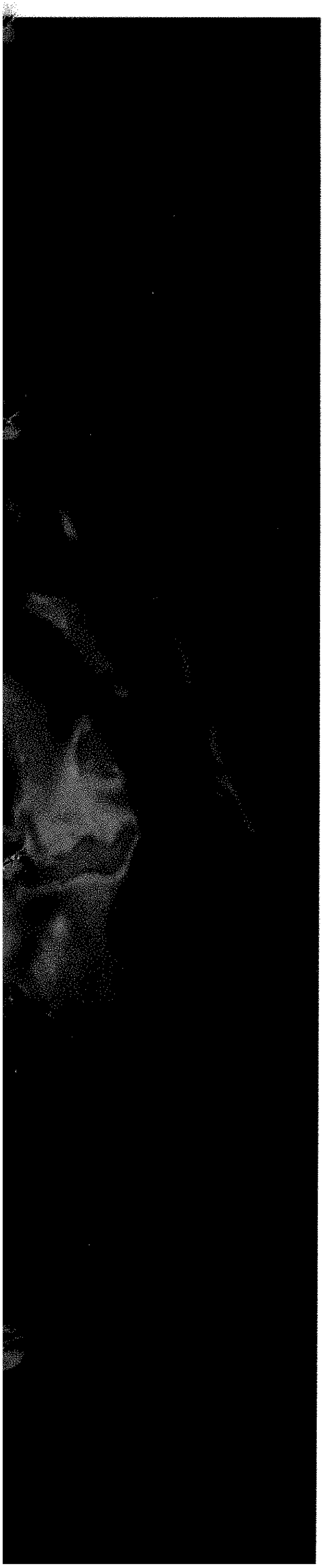

Cholecystitis from the pathogen's point of view

Vibramycin (doxycycline) penetrates gallbladder tissue to reach susceptible[1] pathogens

Vibramycin can be useful in cholecystitis because it provides a wide antibacterial spectrum and therapeutic tissue concentrations.[2] Vibramycin is active against susceptible[1] strains of bacteria including Escherichia coli and Enterobacter aerogenes (formerly Aerobacter aerogenes).

Concentrations of oral Vibramycin in gallbladder tissue removed from four surgical patients on a dosage of 200 mg. P.O. stat and 100 mg. P.O. once daily until surgery.[2]

Patient No.	Concentration in Tissue (mcg./Gm.)
1	5.80[3]
2	1.58
3	8.68
4	7.73

[1] Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

[2] Fabre, J. et al.: Schweiz. Med. Wochenschr. 97:915, May 17, 1967.

[3] Concentration in the bile taken simultaneously: 24.2 mcg./ml.

Vibramycin® I.V.
(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.
200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

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See Brief Summary on following page for information on side effects and contraindications.

Penetrates tissue to reach susceptible* pathogens...

Vibramycin® I.V.
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Important facts about Vibramycin (doxycycline)

- can maintain therapeutic blood levels with a single daily infusion
- can be used without complexities of dosage alteration in patients with impaired renal function
- does not significantly elevate BUN in patients with renal insufficiency
- virtually the same broad range of indications when switching from I.V. to oral form

*Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

Vibramycin® Hyclate (doxycycline hyclate) and
Vibramycin® I.V. (doxycycline hyclate for injection)
BRIEF SUMMARY

Contraindicated: In persons hypersensitive to any of the tetracyclines.

Warnings: Use of tetracyclines during the last half of pregnancy, infancy and childhood to the age of 8 years may cause permanent discoloration of developing teeth. This is more common during long-term use of the tetracyclines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Thus, tetracyclines should not be used in this age group unless other drugs are not likely to be effective or are contraindicated. Individuals receiving tetracycline antibiotics should be advised that direct sunlight or ultraviolet light can cause photosensitivity reactions. If these reactions (exaggerated sunburn) occur, discontinue therapy. Doxycycline forms a stable calcium complex in any bone-forming tissue. Fibula growth has been decreased in prematures given oral tetracyclines 25 mg./kg. q. 6 h., but this reaction was reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

Intravenous Dosage and Administration: Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly nor subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

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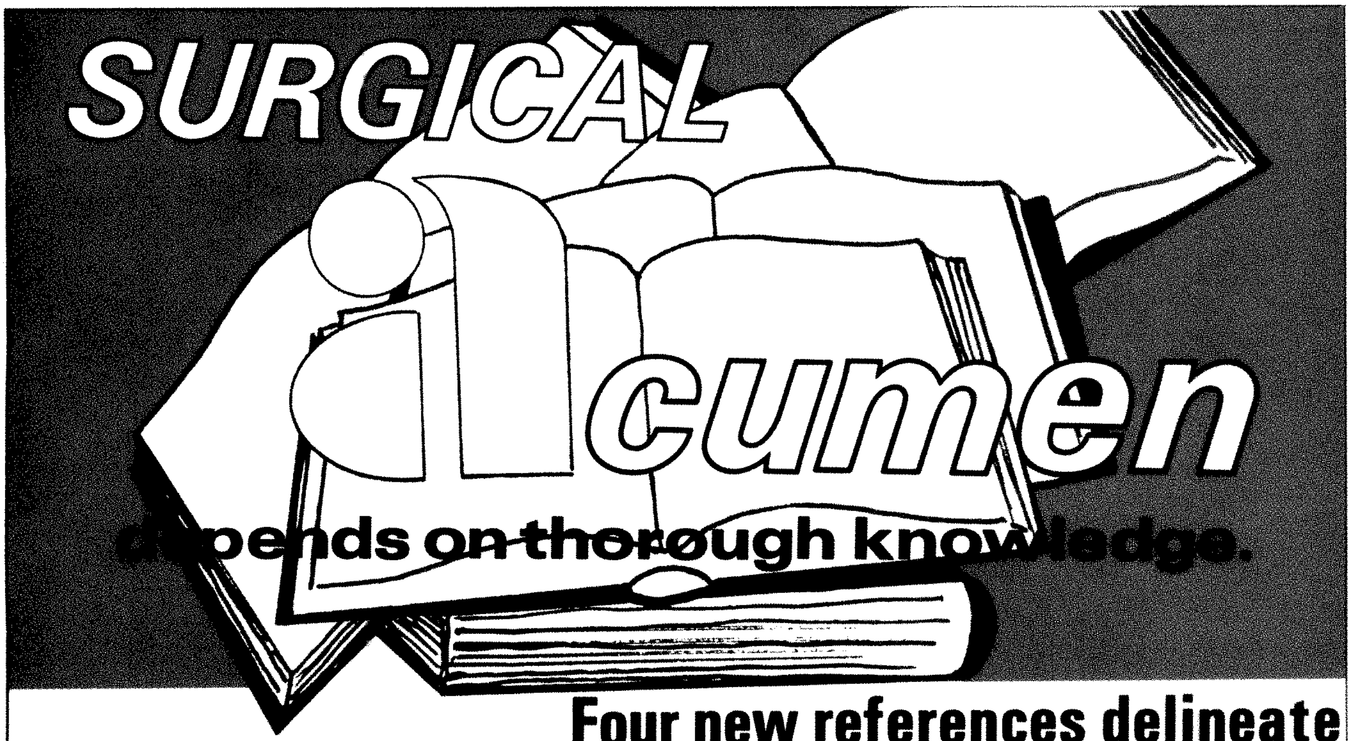

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For severe gram-positive and anaerobic infections*

*due to susceptible organisms

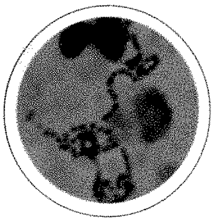
More than 40 investigators participated in initial clinical and bacteriologic studies of Cleocin PO_4. Because it is a parenteral antibiotic, the emphasis was on evaluation of Cleocin PO_4 in serious gram-positive coccal and anaerobic infections. Although there were some cases of mild, uncomplicated infections, most patients were hospitalized and were judged to be moderately to critically ill.

Diagnoses included septicemia and septic shock, acute peritonitis, staphylococcal pneumonia, and massive wound infection. In many cases the infection was secondary to severe accidental trauma, major surgery, or debilitating disease.

Specifically, Cleocin PO_4 has demonstrated antibacterial activity and clinical efficacy in moderate to severe infections due to susceptible strains of the following microorganisms:

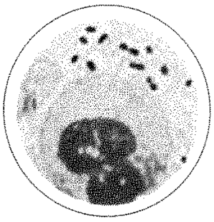
Staphylococci —(*Staphylococcus aureus* and *S. epidermidis* including both penicillinase- and non-penicillinase-producing strains.)

Septicemia, infections of soft tissue, skin, upper and lower respiratory tract.

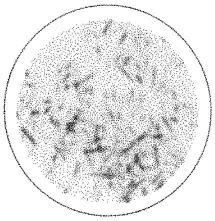


Streptococci—(Streptococci except *Streptococcus faecalis.*)

Septicemia, infections of soft tissue, skin, upper and lower respiratory tract. (Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. Cleocin PO_4 is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cleocin PO_4 in the subsequent prevention of rheumatic fever are not available at present.)



Pneumococci —Upper and lower respiratory infections.



Anaerobic bacteria —(Including species of *Bacteroides, Fusobacterium, Propionibacterium, Eubacterium, Actinomyces, Peptococcus, Peptostreptococcus,* microaerophilic streptococci and *Clostridium.*)

Septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess; infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal-cuff infection; empyema, anaerobic pneumonitis, lung abscess; skin and soft-tissue infections.

For further prescribing information, please see last page of this advertisement.

STERILE SOLUTION

Cleocin® PO4

clindamycin phosphate injection, Upjohn

An injectable antibiotic for staph, strep, pneumococci...

*susceptible strains of the

There are good reasons to consider Cleocin Phosphate (clindamycin phosphate injection) as the initial drug when indicated in moderate to severe infections caused by susceptible strains of staph, strep** and pneumococci.

Clinically and bacteriologically, clindamycin has proved effective in patients with penicillin-resistant staphylococcal infections. Cleocin PO$_4$ is effective against penicillinase-producing staphylococci. However, organisms resistant to clindamycin have been encountered and sensitivity testing should be performed.

Cleocin PO$_4$ is useful in patients who are sensitive to penicillin. Rare cases of sensitivity to clindamycin resulting in maculopapular rash and urticaria have been reported and, as with all antibiotics, it should be used cautiously in atopic patients. However, clindamycin's only demonstrable cross antigenicity is with lincomycin. Thus it can fill a need for both penicillin-sensitive patients and those with penicillin-resistant pathogens.

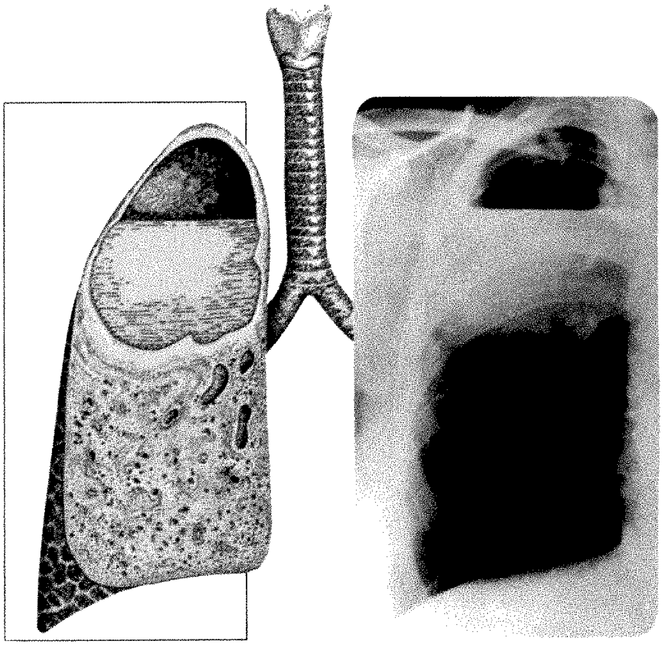
In occasional individuals Cleocin PO$_4$ may cause gastrointestional symptoms including nausea, vomiting and diarrhea. CASES OF SEVERE AND PERSISTENT DIARRHEA HAVE BEEN REPORTED AND HAVE AT TIMES NECESSITATED DISCONTINUANCE OF THE DRUG. THIS DIARRHEA HAS BEEN OCCASIONALLY ASSOCIATED WITH BLOOD AND MUCUS IN THE STOOL AND HAS AT TIMES RESULTED IN ACUTE COLITIS. A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

Useful as initial therapy... with a bonus. Cleocin PO$_4$ is indicated for more than the treatment of susceptible gram-positive organisms.** It has the bonus of activity against anaerobes. For these obscure and potentially lethal pathogens, it may merit early consideration.

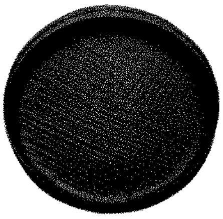
Anaerobes: ubiquitous opportunists. Anaerobes are the dominant population group among the resident flora of the human body. They are abundant in the oropharynx, female genital tract, and in the gut where they constitute 95% of normal fecal flora, out-numbering *Escherichia coli* 1,000 to 1.

Except for *Clostridium,* which became notorious during World War I, anaerobes have often been dismissed as harmless saprophytes. Only recently have they begun to be recognized as a major source of serious infection.

When trauma, surgery, or weakened bodily defenses allow them to spill into the peritoneal cavity, or invade the bloodstream or compromised tissue, they can become lethal opportunists.



When the medium has no message. Anaerobes are the most easily missed category of potentially pathogenic bacteria. Often their presence can only be inferred when a lesion that shows abundant bacteria on a Gram-stained slide yields an apparently sterile culture with routine aerobic methods.



Anaerobes require meticulous collection and special culture techniques. Even a brief exposure to air can kill many of them. Most are fastidious, and they may require as much as ten days' incubation to reveal their presence. In some busy laboratories, plates are discarded prematurely; in others, anaerobic cultures are rarely even made.

The problem of Bacteroides. *Bacteroides* are the most numerous of the anaerobic bacteria and the ones most frequently found in clinically significant anaerobic infections. *Bacteroides* species have been identified in approximately half of surgical infections caused by anaerobic organisms.

Although most *Bacteroides* species are sensitive to penicillin, a frequent exception is *Bacteroides fragilis*—the most commonly encountered pathogen in the genus. This, the most prevalent of anaerobic pathogens, has remained the most difficult to eradicate. Despite antibiotic therapy, *Bacteroides* septicemia has proved fatal in 30% to 40% of patients afflicted.

For further prescribing information, please see last page of this advertisement.
A complete bibliography is available from The Upjohn Company

**Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal pharyngitis and its long-term prophylaxis of rheumatic fever.

and anaerobes*

*pathogens indicated above

Improving the odds against anaerobes. In anaerobic infections the therapeutic significance of Cleocin PO_4 (clindamycin phosphate injection) is best recognized in the context of the seriousness of many of the infections successfully treated. All but one of the clinically and bacteriologically evaluatable patients in the pre-introductory study group had moderate to severe infections. Most had one or more complicating illnesses and, in many, host defenses were severely compromised by traumatic injuries, neoplastic disease, or radical surgery.

Anaerobic infections developed in many as a sequel to massive abdominal gunshot or stab wounds, multiple fractures, or surgery of the gastrointestinal or female genital tract.

Clinical diagnoses included septicemia, deep abscesses of the lungs and various sites in the abdominal cavity and female genital tract, and cases of peritonitis, empyema, endometritis, postsurgical vaginal-cuff infections and anaerobic pneumonitis. In many cases multiple antibiotic regimens, alone or in combination, had failed to control the infection before Cleocin PO_4 therapy was initiated.

Serum levels of clindamycin above the *in vitro* minimum inhibitory concentration for most indicated organisms can be readily achieved and maintained. The minimum inhibitory concentration *in vitro* for anaerobes is generally 1.6 mcg/ml or less.

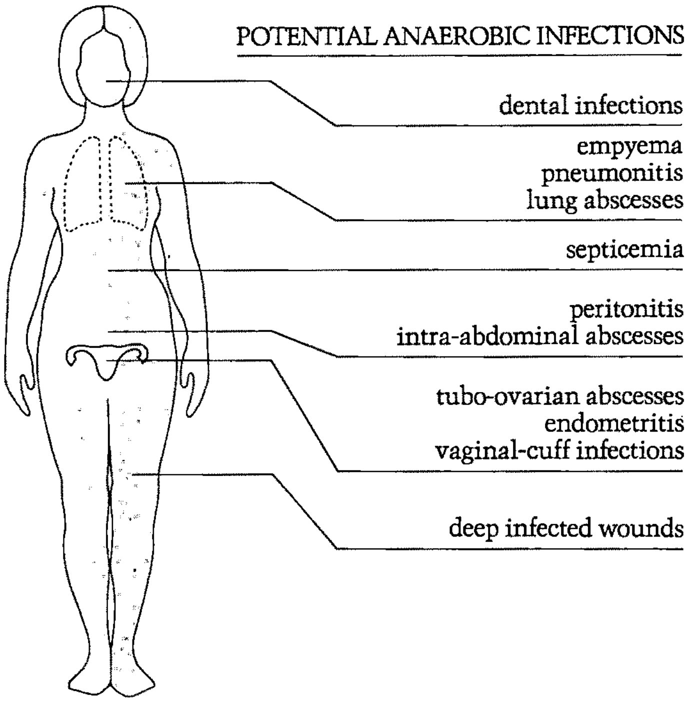
When you suspect an anaerobe. Cleocin PO_4 (clindamycin phosphate injection) is demonstrably effective in anaerobic infections. But with or without the availability of effective antibiotics, the principal problem in managing these infections is recognizing them.

A questioning mind and a sensitive nose are the first and second prerequisites, respectively. Deep necrotic lesions are a potential breeding ground for anaerobes, particularly if located near the oropharynx, the female genital tract, or the gut. Contamination from these areas enhances the risk of infection, as does compromised host resistance. A foul or fecal-smelling lesion or exudate suggests anaerobic infection. Organisms that are visible on the Gram-stained slide but fail to grow on conventional aerobic culture media may be anaerobes.

As with any infection, specimens for culturing and susceptibility testing should be collected before therapy begins. At present, since disc susceptibility testing with present methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility. In severe anaerobic infections, treatment may be started before a definitive diagnosis is made.

If it's a gram-positive coccal infection, there are several alternatives.

If you suspect an anaerobe, consider Cleocin PO_4.



Predictable serum levels... predictably maintained. Cleocin PO_4 is a water-soluble ester of clindamycin and phosphoric acid which hydrolyzes into biologically active clindamycin base within minutes of infusion. Peak serum concentrations of active antibiotic are reached in ten minutes following a 300 mg intravenous dose. With intra-muscular administration, peak levels are achieved within three hours in adults and one hour in children.

Serum levels of clindamycin above the *in vitro* minimum inhibitory concentrations for most indicated organisms can be maintained by administration of clindamycin phosphate every 8-12 hours in adults and every 6-8 hours in children, or by continuous intravenous infusion.

Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease. However, patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy. Elevations of serum transaminases have been observed during therapy with Cleocin PO_4 (clindamycin phosphate injection).

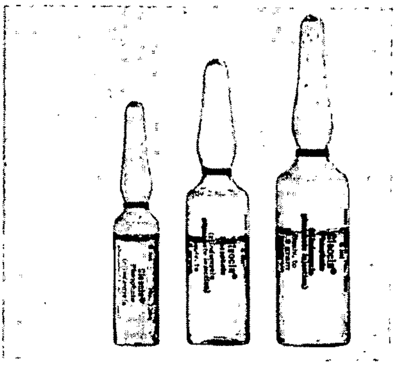
Cleocin PO_4 should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in the Dosage and Administration section of the prescribing information.

STERILE SOLUTION

Cleocin® PO_4

clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE



Effective parenteral therapy against susceptible gram-positive cocci and anaerobes

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Description and Actions: Cleocin Phosphate is a water soluble phosphate ester of clindamycin. Clindamycin is a semisynthetic antibiotic which has greater *in vitro* potency than the parent compound lincomycin. While clindamycin phosphate is inactive, rapid *in vivo* hydrolysis converts it into the antibacterially active clindamycin.

Indications: Cleocin Phosphate is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Streptococci: Upper respiratory-tract infections (Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. Cleocin Phosphate is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cleocin Phosphate in the subsequent prevention of rheumatic fever are not available at present.); lower respiratory-tract infections; skin and soft-tissue infections; septicemia.

Staphylococci: Upper and lower respiratory-tract infections; skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Upper and lower respiratory-tract infections.

Anaerobic bacteria: Lower respiratory-tract infections such as empyema, anaerobic pneumonitis and lung abscess; skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal-cuff infection.

Adjunctive Therapy: In dental infections and in the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies to determine the causative organisms should be performed and their susceptibility to Cleocin tested.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: CASES OF SEVERE AND PERSISTENT DIARRHEA HAVE BEEN REPORTED AND HAVE AT TIMES NECESSITATED DISCONTINUANCE OF THE DRUG. THIS DIARRHEA HAS BEEN OCCASIONALLY ASSOCIATED WITH BLOOD AND MUCUS IN THE STOOLS AND HAS AT TIMES RESULTED IN AN ACUTE COLITIS.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between Cleocin and erythromycin *in vitro.* Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established. *Usage in Newborns and Infants:* When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable. *Usage in Meningitis:* Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of non-susceptible organisms—particularly yeasts. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin phosphate should not be injected intravenously as an undiluted bolus; it should be infused as directed in package insert. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy. In experimental animals, high doses of lincomycin IV have been shown to have neuromuscular blocking properties which are not reversed by neostigmine. Other animal studies have shown that there can be an additive effect or potentiation when lincomycin is given concurrently with d-tubocurarine. There are no studies to this effect with clindamycin phosphate; however, the possibility of this occurring with clindamycin phosphate should be kept in mind due to the chemical similarity of the drug.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. See also under WARNINGS. *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing. *Local Reactions:* Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How supplied: 2, 4 and 6 ml ampoules.

Caution: Federal law prohibits dispensing without prescription.

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STERILE SOLUTION

Cleocin® PO4

clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

Spontaneous Rupture of Hepatoma:

A Misdiagnosed Surgical Emergency

OKOGBUE OKEZIE, M.D., GABRIEL DeANGELIS, M.D.

From The Department of Medicine,
Queens Hospital Center Affiliation of the
Long Island Jewish/Hillside Medical Center,
Jamaica, New York 11432

HEPATOMA, A RARE TUMOR in North America and Europe[4,12] is intimately associated with liver cirrhosis and hemochromatosis,[3] and has a prediliction for middle-aged and elderly men.[4] Antemortem diagnosis is difficult although certain features in a cirrhotic such as abdominal pain, rapid onset of tense bloody ascites, weakness and weight loss, persistent fever unrelated to sepsis, sudden deterioration in a compensated cirrhotic, and the presence of a friction rub have been suggested as clues.[4,6,11,12] There are no pathognomonic signs, symptoms or laboratory indices. The disease mimics other conditions and rarely presents as an acute abdominal catastrophe.[1,4,6] Three apparently well patients who presented with acute abdomen due to spontaneous rupture of a hepatoma form the basis of this report. The unsuspected diagnosis was established at laparotomy.

Case Reports

Case 1. P. A., a 50-year-old black man, presented a 2-week history of right upper quadrant abdominal pain radiating to the right flank. The pain was unrelated to meals or any other bodily functions. For the 2 weeks he was under the care of a private physician who treated him for "inflammation of the liver," with oral medications. There was no improvement and when he noted sudden worsening of his symptoms with nausea and vomiting, he was hospitalized. He had no previous gastrointestinal complaints or trauma. He drank alcohol excessively. On examination he appeared toxic. The blood pressure was 120/80mm Hg. The pulse was feeble, at a rate of 120. The respiratory rate was 26; the temperature 101°F.

The abdomen was moderately distended with marked tenderness on palpation and was rigid and silent. The initial laboratory investigations are shown in Table 1. The clinical impression was an acute abdomen probably secondary to acute pancreatitis. He was observed and treated conservatively. The next day, because of his deteriorating condition, a paracentesis was done, and revealed gross blood in the peritoneal cavity. After multiple blood transfusions, he underwent an exploratory laparotomy. Free blood in the peritoneal cavity was aspirated. The liver was riddled with multiple tumor nodules of varying sizes. The source of bleeding was a cystic, friable mass in the superior aspect of the right lobe which had ruptured. The rest of the abdomen was normal. Multiple biopsies, including the cystic mass, were taken. Hemostasis was secured. The patient died 5 days later in shock. The histological diagnosis was advanced, coarsely, nodular cirrhosis of the liver and hepatoma.

Case 2. Patient J. G., an apparently well 53-year-old Puerto Rican man, was admitted to the Surgical Service on January 12, 1972, because of pain in both legs and bilateral varicose veins of several years duration. Two months previously, at another hospital, he had undergone a left inguinal herniorrhaphy under intravenous anesthesia without incident. On examination he appeared well. The blood pressure was 150/80 mm Hg; the pulse 72 and regular and the respiratory rate 18. The only positive findings were bilateral varicose veins and minimal dependent pitting edema of the lower legs. On January 17, a venogram with hypaque revealed bilateral lower leg varicosities with patency of the deep venous system. The laboratory findings are shown in Table 1. There was no jaundice. On February 7, he was transferred to the Medical Service for further investigation of abnormal liver function tests. A gastrointestinal series was reported as negative, and the liver scan, using colloid, was read as a normal sized liver with changes compatible with cirrhosis. On February 9, he suddenly developed severe right upper-abdominal quadrant and mid-epigastric pain with radiation to the right shoulder. On examination, he was cold and clammy with a blood pressure of 90/70mm Hg; and a feeble pulse of 100. He was afebrile. The abdomen was moderately distended, exquisitely tender to palpation and silent. A flat film of the abdomen showed haziness. The admission hematocrit of 44.7% had dropped to 24%. A diagnostic paracentesis was done and revealed gross blood in the peritoneal cavity. A catheter was left in place. Multiple blood transfusions maintained the hematocrit between 28% and 30%. He continued to leak gross blood and the blood pressure could not be main-

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Submitted for publication January 18, 1973.

Reprint requests: Okogbue Okezie, M.D., Department of Medicine, Queens Hospital Center, 82–68 164th Street, Jamaica, New York 11432.

TABLE 1. *Relevant Laboratory Findings*

Laboratory test	Case 1	Case 2	Case 3
Total bilirubin (0.15–1.0 mg%)	0.7	3	1.5
Alkaline phospate (4–17 K.A.)	12.5	19	47
Albumin (3.5–5 gm %)	3.1	2.5	3.2
Cholesterol (150–300 mg%)	170	153	—
SGOT (15–45 Karmen Units)	25	221	95
Prothrombin time	13.5/13	15/14	—
Glucose (80–120 mg%)	84	80	—
Hematocrit (47 ± 5%)	31%	44.7–24%	28%
Leucocyte (7.8 ± 3 × 10^3)	7,000	5,700	23,000

tained. Despite his poor condition, he underwent an exploratory laparotomy the next day. Approximately 3 liters of blood was aspirated from the peritoneal cavity. The liver was found to contain multiple cysts and a large nodular lesion on the under surface. One of the cysts on the superior surface of the liver had a large rent; obviously the source of the hemorrhage. The cyst was completely unroofed, biopsy of the mass was taken and hemostasis secured. The rest of the abdomen was free of any pathology. The histological diagnosis of both the cyst wall and the other biopsy site was hepatoma and post-necrotic cirrhosis. The post-operative course was stormy. He remained hypotensive, lapsed into coma and died 12 hours later.

Case 3. Patient C. D., a 65-year-old white man was apparently well when he suddenly developed severe right upper quadrant and midepigastric pain with radiation to the right shoulder following supper. There was no fever, jaundice, nausea or vomiting. He denied any previous gastrointestinal symptoms. His symptoms abated sufficiently for him to go to work the following day, but recurred with marked generalized weakness. He denied any alcoholism. On hospitalization on April 13, 1972, he was cold and clammy. The blood pressure was 100/60 mm Hg; and the pulse regular and thready at 100. The respiratory rate was 16. The rest of the examination was unremarkable except for the abdomen which was moderately distended with marked tenderness on palpation of the right upper quadrant with guarding. Bowel sounds were absent. The initial laboratory tests are shown in Table 1. The impression was an acute abdomen secondary to a perforated viscus. A diagnostic paracentesis revealed gross blood in the peritoneal cavity. On April 14, following multiple transfusions he underwent an exploratory laparotomy. Approximately 2½ liters of blood were evacuated. The liver appeared cirrhotic and studded with multiple nodules. There was a nodule over the dome of the liver with a rent approximately 1½ to 2 cm in diameter, the obvious site of the hemorrhage. Several biopsies, including the area of the tear were taken. Hemostasis was secured. The histological diagnosis was cirrhosis of the liver and ruptured hepatoma. He was discharged on the twenty-third hospital day for supportive care at home.

Discussion

These 3 cases would not be unusual in the Orient and in some African countries where spontaneous rupture is not an unusual mode of presentation of hepatomas.[1] In his classical monograph, Berman[4] reported 6 cases of "acute abdominal cancer," in Bantus. Ong *et al.*[9] described 20 such cases in a 3-year period in Hong Kong. The susceptibility of the Chinese to hepatomas has been alluded to by Strong and Pitts.[13]

Cases of spontaneous rupture of a hepatoma in the West have been limited to case reports. Some have occurred as a terminal complication in a decompensated cirrhotic. Most have been accidental findings at necropsy.[11,12]

Kew Mc *et al.*[6] have demonstrated the feasibility of antemortem diagnosis by diagnosing hepatomas during life in 63% of 75 patients in a 10-year period. Two patients presented with acute abdomen due to spontaneous rupture.

The 3 cases presented here are unusual in that rupture occurred in apparently well individuals. The diagnosis was unsuspected prior to rupture. Laboratory findings were non-specific. The diagnosis was made by paracentesis and exploratory laparotomy. Patients 1 and 2 had cystic lesions, biopsies of which were histologically hepatomas. We are not aware of the association of cystic lesions of the liver with hepatomas. This apparent association warrants further study. Patient 3 was not an alcoholic, but all 3 demonstrated cirrhosis at biopsy. All were men, reflecting a well known predominance of males. Some authors[5,7] have alluded to the rising incidence of hepatomas in the Western world. If this proves true, this mode of presentation may become more common and should be considered in the differential diagnosis of the acute abdomen.

The hepatic artery provides the main blood supply to the primary tumor. It has been shown that small vessels within the tumor are tortuous and dilated and are functionally arterio-venous anastomoses. Wartnaby *et al.*[14] have demonstrated increased intrahepatic shunting through the tumor. Since hepatomas are very vascular, it is conceivable that a surface tumor could rupture from a trivial trauma. But trauma has not been a prominent feature in these patients. Rupture may also occur from the center of a necrotic tumor by erosion of the blood vessels.[4,5] Cystic lesions may rupture from increased intrahepatic vascular tension. It is rather intriguing that ruptures are not more frequent. The sudden onset of abdominal pain in a compensated or decompensated cirrhotic with signs of an acute abdomen makes paracentesis imperative. If gross blood is obtained, treatment consists of blood replacement and an immediate exploratory laparotomy. Attempts should be made to enucleate the bleeding tumor, if feasible, and establish hemostasis. The prognosis, which remains bleak, is determined by the time of diagnosis, the degree of hemorrhage and the basic disease. In the series of Ong *et al.*,[9] only 2 patients lived for more than 6 months. Our third patient is still alive, though with progressive disease.

References

1. Alpert, M. E., Hutt, M.S.R., Davidson, C. S.: Primary Hepatoma in Uganda. Amer. J. Med., **46**:794, 1969.
2. Benner, E. J., Labby, D.: Hepatoma: Clincial Experience with a Frequently Bizarre Tumor. Arch. Intern. Med., **54**:620, 1961.
3. Berk, J. E., Lieber, M. M.: Primary Carcinoma of the Liver in Hemachromatosis. Amer. J. Med. Sci., **202**:708, 1941.
4. Berman, C.: Primary Cancer of the Liver. London, Lewis, 1951.
5. Hoyne, R. M., Kernohan, J. W.: Primary Carcinoma of the Liver: A Study of Thirty-one Cases. Arch. Intern. Med., **79**:532, 1957.
6. Kew, M. C., Das Santos, H. A., Sherlock, S.: Diagnosis of Primary Carcinoma. Br. Med. J., **4**:408, 1971.
7. Mac Donald, R. A.: Primary Cancer of Liver. A Clinicopathological Study of 108 Cases. Arch. Intern. Med., **99**:226, 1957.
8. Mast, W. H., Steamer, C. W.: Primary Carcinoma of the Liver with Spontaneous Rupture. JAMA, **100**:1684, 1933.
9. Ong, C. B., Chu, E. P. H., Yu, F. Y. K., et al.: Spontaneous Rupture of Hepato-cellular Carcinoma. Br. J. Surg., **52**: 123, 1965.
10. Patton, R. B., Horn, Jr., R. C.: Primary Liver Carcinoma: Autopsy of Sixty Cases. Cancer, **17**:757, 1964.
11. Schnabel, T. G.: Primary Carcinoma of the Liver with Spontaneous Rupture and Lethal Hemorrhage. Ann. Surg., **101**:613, 1935.
12. Sherlock, S.: Diseases of the Liver and Biliary System. 4th ed. Philadelphia, F. A. Davies Co., 651, 1968.
13. Strong, G. F., Pitts, H. H.: Primary Carcinoma of the Liver. Arch. Intern. Med. **46**:105, 1930.
14. Wartnaby, K. M., Bouchier, I. A. D., Pope, Ce. ll, et al.: Hepatic Blood flow in Patients with Tumors of the Liver. Gastroenterology, **44**:733, 1963.

Lung Autografts:

Long Term Functions

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APART FROM REJECTION, transplantation of the lung creates a number of anatomical alterations such as total denervation, interruption of lymphatic drainage and lack of bronchial blood supply. These, together with operative trauma, affect lung function. Since we were interested in separating the acute physiological effects of the surgical procedure from immunological injury, long term autotransplants were studied.

Several investigators have reported that autotransplanted lungs suffer a moderate impairment of ventilation, a significant decrease in oxygen uptake, a reduction of pulmonary blood flow, and late pulmonary hypertension.[5,9,13,16,18,19] In some animals the functional impairment was produced by anatomical defects of the reimplanted lung, such as stricture of arterial, venous and bronchial anastomoses.[2] Most of the previous studies on autotransplanted lungs measured only few respiratory functions, and correlation with postmortem findings was commonly lacking. Therefore, this report is a comprehensive study using the most common functional tests, correlated with the anatomopathologic findings at autopsy to assess the effects of the autotransplantation procedure over a 4-year period of follow up.

Because the techniques to measure pulmonary functions were intended for use with alert, cooperative human subjects, these methods were modified for use with general anesthesia in the animal studies. The following tests were adapted for the anesthetised animals: Differential ventilation, lung compliance, total lung capacity, functional reserve capacity, oxygen uptake, diffusion capacity for CO, and pulmonary hemodynamics with all the cardiac output directed to the autotransplanted lung. The techniques and results of these studies are the basis for this report.

Materials and Methods

Eight dogs with the left lung autografted 4 years previously were studied. Their weight ranged from 15 to 27.5 kg. and varied little for each animal during the 4 years of observation. Six weeks following the operative procedure, bronchospirometry was performed to ascertain that the autotransplanted lung was functioning. At the same time the condition of the bronchial anastomosis was assessed by bronchoscopy. Each of the animals had demonstrable ventilation and oxygen uptake of the autotransplanted lung and a patent, well-healed bronchial anastomosis. However, the animals were not selected for the quality of their functions. The presence of any oxygen uptake and ventilation of the autotransplant was enough to include the animal in the study group. Only one animal among all the survivors was rejected because of severe bronchial stricture.

The technique of the reimplantation was as follows: The left lung was excised with an atrial cuff attached to the pulmonary veins and irrigated with cold (4°C), heparinized lactated Ringer's solution until the fluid coming from the pulmonary veins was clear of blood (about 500 ml. of solution was needed). The atrial cuff was reattached with a continuous everting 5-0 silk suture.

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The main bronchus was anastomosed with continuous 3-0 chromic catgut and the pulmonary artery with continuous 6-0 silk. The lung ischemia lasted approximately one hour. The animals were anticoagulated postoperatively with heparin for 48 hours and then with Dicumarol for 3 weeks. The prothrombin time was maintained between two and three times control value. Daily injections of penicillin (500,000 U.) and streptomycin (0.5 gm.) were given postoperatively for 5 days. The dogs were kept in the chronic section of our animal facilities. They were in excellent health and did not require special care.

Bronchospirometric determination of the function of each lung was performed on several occasions with a double lumen plastic catheter previously described.[10] The dogs were premedicated with atropine, anesthetized with thiopental sodium (15 mgm/Kg.), and positioned on their backs in a negative pressure respirator of our design. The trachea was anesthetized topically with 1% pontocaine and the bronchial divider was introduced. Proper position of the tube and separation of each lung from the other was assured by observing the tracing of the twin spirometer and by adding pressure on one spirometer bell and observing if any leak developed in the system, manifested by a change in the spirometric tracing base line when the pressure was released.[1] Measurement of the tidal volume (Vt), minute ventilation ($\dot{V}$m) and oxygen uptake ($\dot{V}O_2$) were performed with the animal breathing spontaneously using the twin spirometer.* To be sure that the ostium of the left upper lobe was not obstructed by the left arm of the bronchospirometric tube, the position of the tube was reversed (the left arm was placed in the right bronchus) and the $\dot{V}O_2$ and $\dot{V}$m were again measured. This manuever was carried out in several studies. but was discontinued when no significant difference in the oxygen uptake and the ventilation of the left lung could be found between the reversed and normal position.

Following the determination of ventilation and oxygen uptake, an esophageal balloon was placed in the lower third of the esophagus and connected to a pressure transducer. The animal's spontaneous breathing wan stopped with succinyl choline (approximately 0.5 mgm./kg.) and mechanical ventilation was started with the body respirator. Expiration was made to last twice as long as the inspiration. The tidal volume was arbitrarily selected to correspond to twice the predicted normal value.[12] To avoid alveolar collapse each lung was manually hyperinflated with about double the selected tidal volume immediately before each measure of compliance.[14]

The air flow from each lung was measured with a pneumotachograph* and was integrated electrically† into volume. The transpulmonary pressure was measured with the esophageal balloon and a pressure transducer.‡ Flow, volume and pressure were recorded with a direct writing polygraph.§ Lung compliance was calculated at the point of zero flow, from the tidal volume and the transpulmonary pressure tracing (Fig. 1). Each value is the mean of 4 determinations. Bilateral lung compliance was measured following the unilateral de-

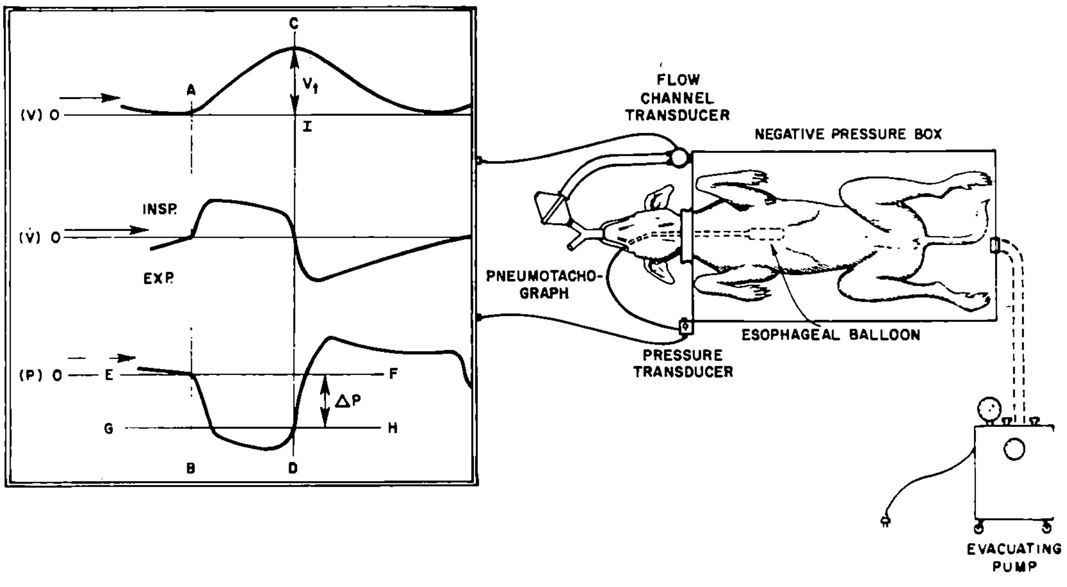

FIG. 1. Determination of lung compliance. The animal is in the negative pressure respirator anesthetized, paralyzed and mechanically ventilated. A double lumen bronchospirometric tube is in position. The transpulmonary pressure (P) is measured through an esophageal balloon with a pressure transducer. The respiratory flow (V) is measured with a pneumotachograph and integrated electrically into volume (V). Compliance is calculated with the formula $C = Vt/\Delta P$. Tidal volume (Vt) and differential pressures (Δp) are obtained from volume and pressure tracings of the point of zero flow.

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* Pulmotest, N. V. Godart, Debilt, Holland.

* Hewlett-Packard, Palo Alto, Calif.

† Respiratory preamplifier 350-5000B, Hewlett-Packard, Palo Alto, Calif.

‡ Pressure transducer 268B, Hewlett-Packard, Palo Alto, Calif.

§ Recording System 7714A, Hewlett-Packard, Palo Alto, Calif.

terminations, using the same bronchospirometric tube but joining both lumens with a "Y" connector. One set of determinations lasted 5–6 minutes.

Total lung capacity (T.L.C.) and functional reserve capacity (F.R.C.) for each lung separately and both lungs simultaneously were measured. With the animal remaining anesthetized and paralyzed, the negative pressure in the respiratory box was regulated to produce a miximum negative transpulmonary pressure of −15 cm H_2O during breath holding. However, this degree of negative transpulmonary pressure was not achieved during the respiratory cycle. This setting usually provided a minute ventilation moderately larger than the normal predicted value. The F.R.C. was measured at the ventilatory level created by this arrangement, employing a closed circuit helium dilution method and a volume-stabilized spirometer with mixing pumps[‖] (Fig. 2). The test began at the end of a normal expiration and continued for approximately 3 minutes, which usually was one minute more than the time necessary for equilibration. Helium was analyzed with a catharometer,[*] and the functional reserve capacity was calculated with the following formula:

$$\mathrm{FRC} = \frac{F_IHe - F_EHe}{F_EHe} \times \mathrm{SV}$$

When F_IHe is the initial helium concentration in the spirometer, F_EHe is the final concentration in the system and SV = spirometer volume at the start of the determination.

The total lung capacity was calculated by adding the F.R.C. to the inspiratory capacity obtained with a negative transpulmonary pressure of −15 cm H_2O, maintained until no volume increase was recorded in the spirometer tracing.

Diffusion capacity for CO was measured with the single breath technique of Ogilvie, *et al.*,[15] modified for use in dogs as follows: One of the bells of the twin spirometer was filled with the experimental gas mixture (0.3% CO, 10% He, 20% O_2 and the rest N_2). One of the lumens of the bronchospirometry tube was connected to the spirometer with a short "y" tubing (dead space less than 10 ml.), one arm of the "y" tube was joined by tubing to an empty one liter rubber collecting bag and the tubing clamped. Breath holding was accomplished by maintaining the negative pressure in the body ventilator for 10 seconds. The breath holding period was suddenly interrupted by disconnecting the ventilator box from the source of negative pressure; the sudden drop of negative pressure produced a rapid expiration. The first one-third to one-half of the tidal volume was

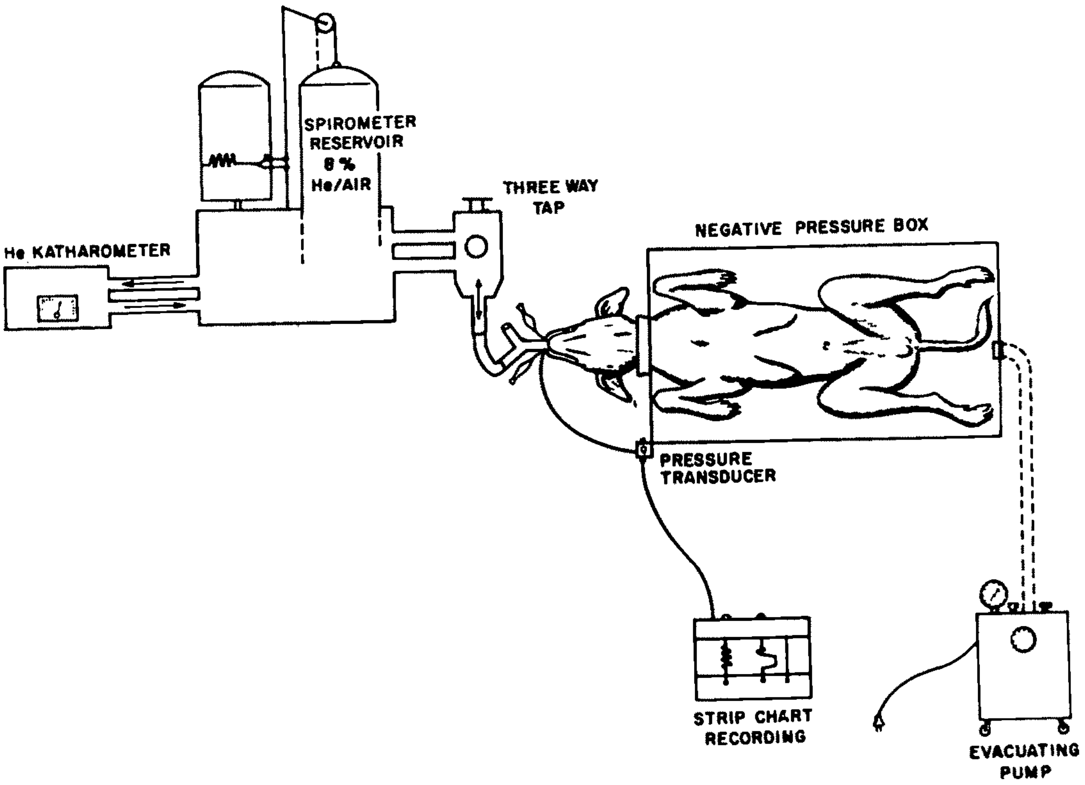

Fig. 2. The determination of functional reserve capacity of each lung. The animal was ventilated in the negative pressure respirator. A bronchospirometric tube is in place. The F.R.C. was measured using helium (8%) with a closed circuit technique. The test began at the end of the normal expiration and continued for about three minutes to allow complete mixing of the spirometric gas mixture and the lung gas. Formula for calculation is in the text.

[‖] Pulmotest, N. V. Godart, Debilt, Holland.

[*] Helium Catharometer P-490, Warren E. Collins, Inc., Braintree, Mass.

allowed to escape, and the remainder of the expiratory volume was collected in the sampling bag by clamping the tube going to the spirometer and unclamping the other tubing attached to the sampling bag. A sufficient volume of gas was collected to measure the carbon monoxide concentration with an infrared analyzer* and the helium concentration with a catharometer connected in series (see diagram of circuit in Fig. 3). The diffusion capacity was measured 3 times in each lung and twice bilaterally; the value given is the mean of those determinations. The calculation of DLCO was done with a standard modification of the classic equation of Krogh.

$$\mathrm{DLCO} = \frac{VA \times 60}{(PB - 47)t}\, ln \left[\frac{F_ICO \times F_eHe}{F_ECO \times F_IHe}\right]$$

VA is the alveolar volume = functional reserve capacity (F.R.C.) plus inspiratory capacity (I.C.). *PB* is the barometric pressure, *t* is the time of breath holding in seconds, F_ICO is the carbon monoxide concentration of the inspired gas, F_ECO is the carbon monoxide concentration of the expired gas, F_IHe is the helium concentration of the inspired gas, F_EHe is the helium concentration of the expired gas and *ln* is the natural logarithm. The duration of breath holding was accurately measured in the recording of the transpulmonary pressure curve from the start of the inspiration to the beginning of the expiration.

Pulmonary hemodynamics were measured between the first and second year following transplantation (mean 15.8 months). A right heart catheterization was performed with the animal under thiopental anesthesia, intubated, and mechanically ventilated. The main pulmonary artery pressure (PA), cardiac output ($\dot{Q}$) by dye dilution were measured, and total pulmonary vascular resistance calculated before and following occlusion of the right pulmonary artery. A triple lumen catheter with a balloon at the tip was used to occlude the right pulmonary artery.

Of the original 8 animals in the group, one was sacrificed 2 years later because it developed a laryngeal stricture and another died 38 months following the transplantation of a perforated gastric ulcer. In both animals the autotransplanter lungs were grossly normal. The other 6 animals were kept for an average period of 4 years. A few days following the last pulmonary function studies, a right pneumonectomy was performed. Pulmonary artery, left atrium and aortic pressures were measured with the chest open before and after pneumonectomy. Two animals survived the procedure and were sacrificed 2 months later.

A group of 6 normal dogs was tested with the same equipment and techniques as the autotransplanted group. The mean values of those determinations were used as normal controls.

Results

A summary of the gross and microscopic findings of the autografted lung is presented in Table 1. Special attention was paid to the vascular and bronchial anasto-

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* Infrared Analyzer #IR15A- Beckman Instruments, Inc. Fullerton, Calif.

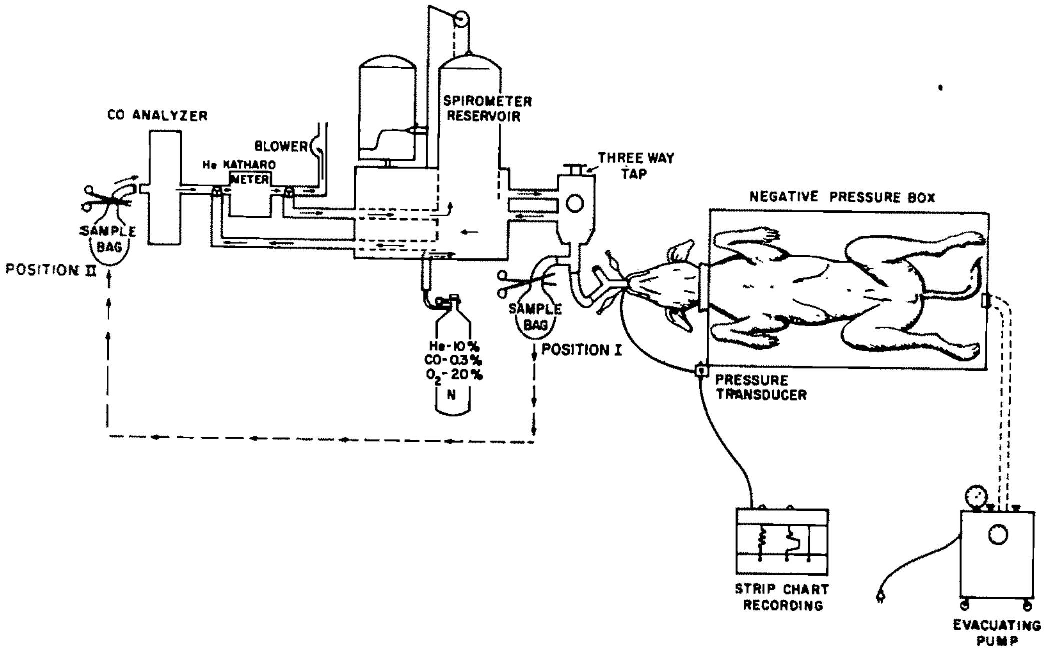

FIG. 3. The determination of differential diffusion capacity for carbon monoxide with the single breath holding technique. The animal is anesthetized and paralyzed. A ten-second inspiratory breath holding is achieved by maintaining a transpulmonary pressure of −15 cm H_2O. The dog inspires a gas mixture containing 10% helium, 0.3% carbon monoxide, and 20% oxygen, in nitrogen. The last two-thirds of the expiratory volume are collected in a sample bag. The concentration of carbon monoxide and helium in the sample bag are measured with an infrared analyzer and a catharometer assembled in series. The formula used for calculation of DLCO is in the text.

TABLE 1. *Lung Allografts: Pathologic Findings*

Dog #	Anastomosis			Lung	Comments
	Pulmonary Artery	*Atrium*	*Bronchus*		
A-1	Open 25 mm circumference normal	Common atrial anastomosis 85 mm circumference	Open, 50 mm circumference. Normal microscopic	Minimal pleural adhesions Upper lobe areas of focal emphysematous blebs. Normal vessels	Survived pneumonectomy. Sacrified one month later
A-2	Intact. Silk suture granuloma 22 mm circumference	Unremarkable. Sup. pulm. vein 18 mm Inf. pulm. vein 32 mm	Open 47 mm. circumference. Submucosa fibrosis and ossification of cartilage	Multiple pleural adhesions. Venous congestion. Vessels of small calibre	Died of respiratory insufficiency following pneumonectomy when on respirator.
A-3	Open, 16 mm. circumference, some scarring suture site.	Sup. pulm. vein 13 mm Inf. pulm. vein 22 mm Fibrosis and suture material	63 mm. circumference Disarray cartilage and rings	Multiple adhesions. Pleural fibrosis and emphysema upper lobe. Intimal proliferation and fibrosis present in small pulmonary vessels	Died 2 hours following pneumonectomy Cardiac arrhythmia
A-6	Circumference 24 mm. Ossification at anastomotic site	Sup. pulm. vein 24 mm. Inf. pulm. vein 22 mm. Some scarring at suture site	36 mm. circumference Obstruction L.U.L. bronchus	Atelectasis L.U.L. Normal lower lobe. Small calibre pulmonary vessels with hyperplastic changes	Died 3 hours following pneumonectomy of respiratory failure
A-7	Circumference 25 mm Normal	Common atrial anastomosis 47 mm. circumference.	26 mm. circumference Fibrosis suture line	Extensive pleural adhesions with pleural fibrosis. Small calibre vessels	Died 10 hours post-pneumonectomy of probable respiratory insufficiency
A-8	Circumference 34 mm Calcification at anastomotic site	Common atrial anastomosis. 64 mm circumference	45 mm. circumference. Normal microscopic	Minimal upper lobe pleural adhesions. Normal microspic	Survived pneumonectomy. Sacrificed two months later.

moses. All anastomoses were well healed and patent. The circumference of the bronchial and pulmonary artery anastomoses were 2 mm. less than the circumference measured 5 mm. proximally, and the same as the circumference 5 mm. distally. Microscopic calcification, granulomatous formation and some scarring were commonly seen at the vascular suture site. However, no evidence of narrowing was detected. The bronchial anastomoses were widely open, but ossification and disarray of cartilages were occasionally seen. One animal (A-6) had obstruction of the left upper lobe bronchus with distal atelectasis. Variable degrees of pleural fibrosis were observed in all specimens. In 2 animals (A-3, A-6) the distal branches of the pulmonary arteries showed reduced lumen size, mild intimal proliferation and hyperplastic changes.

Three animals died a few hours following the right pneumonectomy with cardiac arrhythmias and respiratory failure in spite of being mechanically ventilated. The other death occurred 10 hours later when the animal was breathing spontaneously and apparently doing well. Neither of the 2 survivors had postoperative problems or complications.

At the cardiac catheterization 16 months after autotransplantation, the mean pulmonary pressure (18 ± 4.8 mm Hg.) increased slightly when the right pulmonary artery was occluded (20.8 ± 5.9 mm Hg.) and all the cardiac output was diverted through the autotransplanted lung (Fig. 4). However, larger increases in pulmonary pressures were found in normal dogs when all the flow was diverted to the left lung (from 17.83 ± 6.37 mm Hg. to 26.67 ± 6.7 mm Hg.). Total pulmonary vascular resistance (TPR) was higher in the autografted dogs (8.2 ± 2.2 mm Hg/ml/sec./Kg.) than in the control group (4.8 ± 1.5 mm Hg/ml/sec./Kg.). The increase in TPR after occlusion of the right pulmonary artery was similar in the dogs with an autotransplanted left lung to that observed in the control

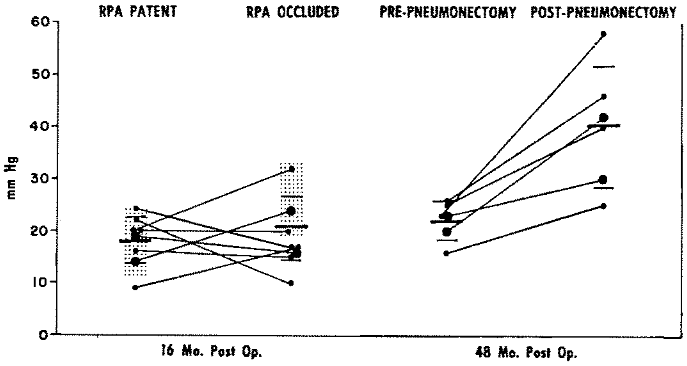

FIG. 4. The pulmonary artery pressure by cardiac catheterization (16 mos. postop) with the right pulmonary artery (R.P.A.) patent and occluded. Each animal is represented by a dot. The larger dots are the survivors following contralateral pneumonectomy. The horizontal lines are the mean ± one standard deviation of the autotransplanted group. Shaded areas represent mean ± one standard deviation in 6 normal dogs. The pulmonary artery pressures before and after right pneumonectomy are shown.

group. Two-and-a-half years later, when the pulmonary artery was ligated performing the pneumonectomy, the pulmonary artery pressure was again measured with the chest open. The mean PA pressure before ligation was similar to the previous measurement. However, on ligating the right pulmonary artery there was a significant increase in pressure. No correlation was found with the elevation of the pulmonary pressure and the survival of the animal following pneumonectomy (Fig. 5).

The mean minute ventilation ($\dot{V}$m) of 7 long autografts measured under spontaneous breathings was 0.935 ± 0.297 L./min. 32 months following the surgical procedure (Table 2, Fig. 6). At this time the right or normal lung had a $\dot{V}$m of 1.666 ± 0.277 L./min. Therefore, the autograft contributed 36% of the total ventilation. One-and-a-half years later the mean $\dot{V}$m. of 6 lung autografts increased to 1.22 ± 0.565 L./min. The $\dot{V}$m of the normal lung was 1.761 ± 0.609 L./min. The autograft at 48 months contributed 41% of the ventilation. Since the ventilation of the anesthetized spontaneously breathing animals depends on the level of the anesthesia, absolute values are not meaningful; the ventilation relationship between the lungs gives a better idea of the functional capacity of each lung. In our 6 control animals the mean left lung minute ventilation was 1.229 ± 0.533 or 38% of the total; however, the contribution of each lung to the total ventilation varies considerably, as seen by the large standard deviation. The mean value for ventilation of the autografted lung was not significantly different from that for the normal left lung. It was within

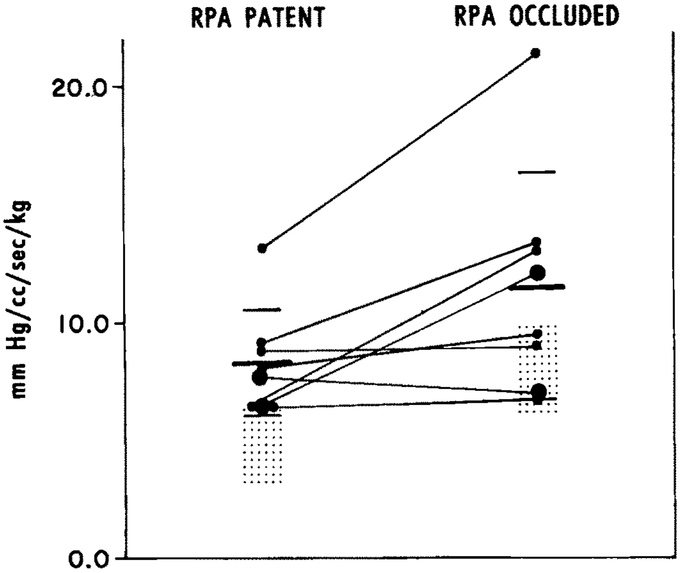

FIG. 5. Total pulmonary vascular resistance calculated from cardiac catheterization at 16 months postoperatively with the right pulmonary artery open and occluded. Symbols are the same as used.

TABLE 2. *Lung Autografts: Long Term Functions Summary of Data*

Group	No. Dogs	Lung	Wt (Kg.)	$\dot{V}$M (L/min.)	T.L.C. (L.)	F.R.C. (L.)	FRC/TLC	C (L./cm H_2O)	$\dot{V}O_2$ (L./min.)	DLCO (ml./min./mm Hg)
Auto Transplant 32 mos.	7		23.4							
			±3.1							
		Rt.		1.666	1.44	0.73	.50	0.053	0.081	15.6
		SD		+0.277	+0.39	+0.21		0.016	0.011	±2.9
		Lt.		0.935 (36)	0.65 (31)	0.27 (27)	.41	0.027 (34)	0.032 (28)	6.7 (30)
		SD		±0.297	±0.18	±0.08		0.007	0.014	±2.8
		Bil		—	2.15	1.01	.47	0.078	—	24.1
		SD		—	±0.51	±0.29		0.022	—	±3.5
48 mos.	6		22.6							
			±3.7							
		Rt.		1.761	1.44	0.69	.48	0.053	0.075	12.9
		SD		±0.609	±0.33	±0.19		0.015	0.015	±2.2
		Lt.		1.220 (41)	0.74 (34)	0.34 (33)	.46	0.027 (34)	0.029 (28)	5.7 (31)
		SD		±0.565	±0.14	±0.10		0.008	0.015	±1.4
		Bil		—	2.17	0.98	.45	0.079	—	18.7
		SD		—	±0.36	±0.14		0.020	—	±1.4
Control	6		23.5							
			±5.0							
				2.023	1.28	0.59	.46	0.051	0.068	10.0
				±0.720	±0.14	±0.10		0.002	0.006	±3.0
				1.229 (38)	0.83 (39)	0.37 (38)	.45	0.031 (38)	0.040 (37)	6.6 (40)
				±0.533	±0.20	±0.09		0.020	0.009	±3.2
				—	2.09	0.96	.46	0.083	—	17.0
				—	±0.28	±0.14		0.025	—	±5.9

( ) percentage of bilateral function
$\dot{V}$m = minute ventilation
$\dot{V}O_2$ = oxygen uptake per minute
T.L.C. = total lung capacity
F.R.C. = functional reserve capacity
C = lung compliance
DLCO = pulmonary diffusion capacity for CO

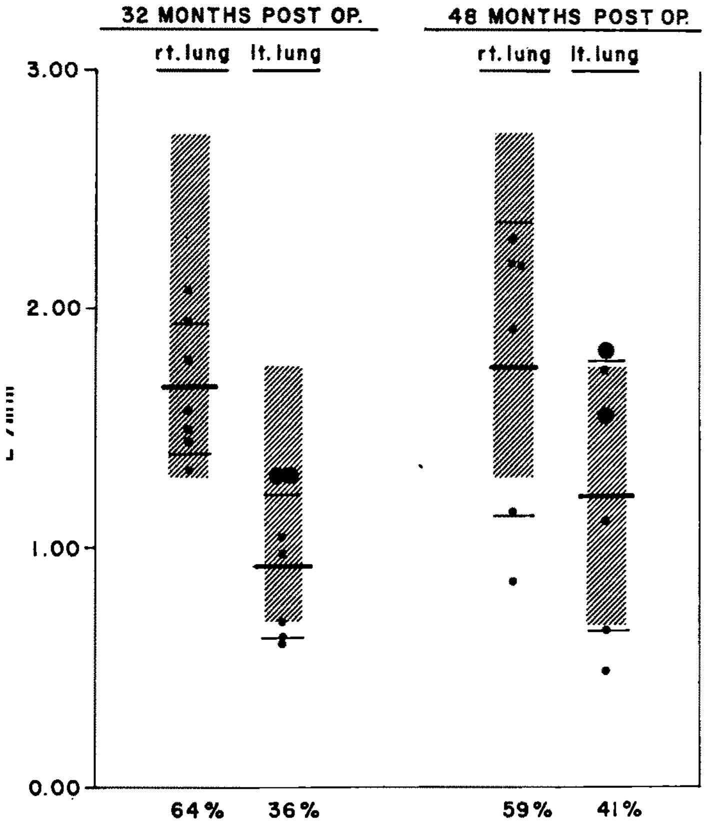

FIG. 6. The minute ventilation at 32 and 48 months postoperatively of right (normal) and left (autotransplant) lungs. Dots represent each individual dog. Larger dots represent the 2 dogs that survived right pneumonectomy. Mean ± one standard deviation is indicated by horizontal lines. Shaded bars indicate ± one standard deviation from the mean values of 6 normal control dogs. The mean percentage of the contribution of left and right lungs to the total function is shown in the bottom of the figure. These symbols are used in Figs. 7–11.

normal ranges when compared with the control group. No significant changes were observed during the four year study period.

Total lung capacity (T.L.C.) for the autograft at 32 months was 0.65 ± 0.18 L. (Fig. 7). The right lung had a T.L.C. of 1.44 ± 0.39 L. The autograft contributed 31% of the total lung capacity. The bilateral T.L.C. as measured was 2.15 ± 0.51 L.; there was less than 5% difference between the sum of the right and left lung capacities and the measured T.L.C. Sixteen months later, the right T.L.C. remained unchanged in the 6 surviving animals; the autograft lung showed a slight increase compared to the previous value (0.74 ± 0.14 L.). Again the bilateral measured T.L.C. was within 5% of the sum of the T.L.C. of each lung, indicating that the technique was easily reproducible. The left lung in the control animals contributed 39% of the bilateral total lung capacity.

The functional reserve capacity of the autotransplanted lung at 32 months was 0.27 ± 0.08 L. which represents 27% of the mean bilateral F.R.C. (Fig. 8, Table 2). The left lung F.R.C. in the control animals was 38% of the mean bilateral value. One-and-a-half years later the transplant F.R.C. was 0.34 ± 0.10 or 33% of the total F.R.C., a value very similar to that of control dogs. Perhaps more important than the actual value of F.R.C. is the relationship between functional reserve capacity and total lung capacity. Those ratios were not significantly changed on the autotransplanted lung at 48 months (.46) as compared with the control group. However, at 32 months, the autotransplanted lung FRC/TLC was somewhat smaller than control.

At 32 months the mean compliance of the right lung was 0.053 ± 0.016 L./cm H_2O (Fig. 9). The left lung compliance was 34% of the sum of both lungs. Sixteen months later the surviving 6 animals had the same mean compliance for the right and left lungs. In the control group, the right lung compliance was 0.051 ± 0.002 L./cm H_2O and the left lung was 0.031 ± 0.020 L./cm H_2O. The bilateral lung compliance was 0.083 ± 0.025 L./cm H_2O. Compliance depends upon the size of the animal; however, the mean weight of both groups of dogs was almost identical. The small difference between the autograft and the control is not statistically significant ($P > 0.20$).

The oxygen uptake per minute ($\dot{V}O_2$) 32 months following the autotransplantation procedure was 0.081 ± 0.011 L./min. for the right lung and 0.032 ± 0.14 L./min. (28% of the total $\dot{V}O_2$) for the autotransplanted lung (Fig. 10). At 48 months the right lung had an oxygen uptake of 0.075 ± 0.015 L./min. and the autograft, 0.029

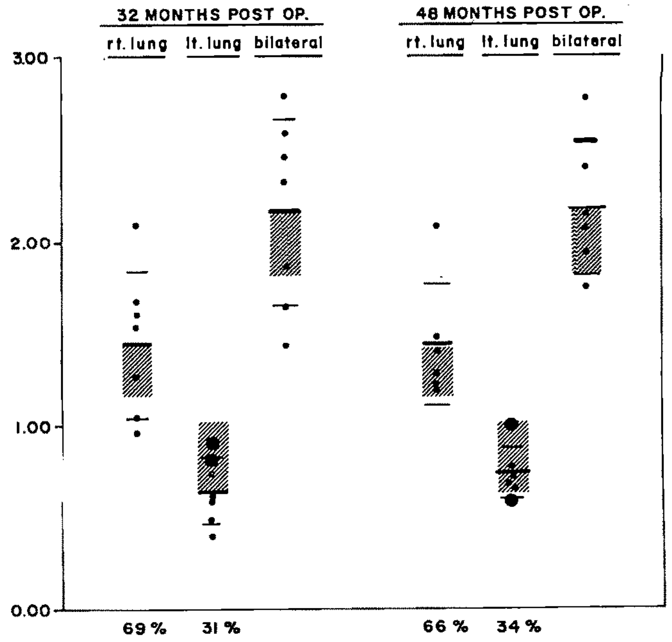

FIG. 7. The total lung capacity of the left autografted lung, right normal lung and bilateral measurement.

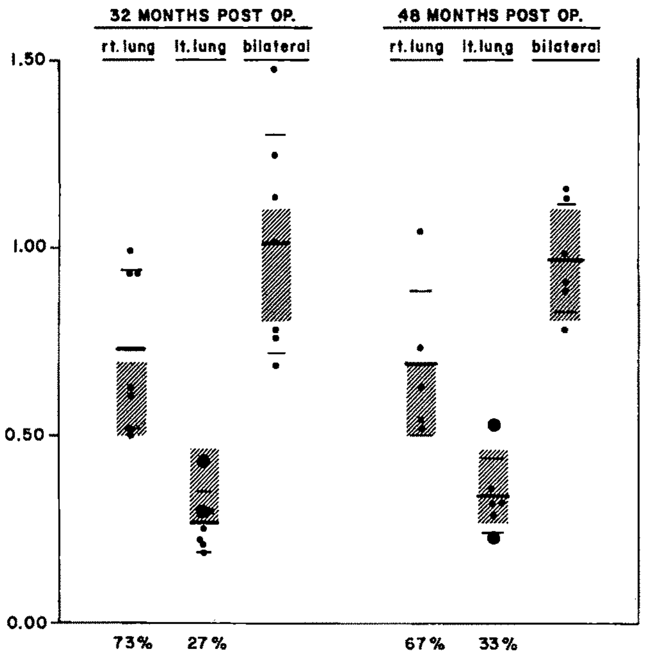

FIG. 8. Individual lung and bilateral functional reserve capacity following autografting.

± 0.015 L./min. (28% of the total $\dot{V}O_2$). In the control group the left lung had a mean $\dot{V}O_2$ of 0.040 ± 0.009 L./min. (37% of the total $\dot{V}O_2$, which is larger than that of the autografted lung, but not statistically significant ($P > 0.1$). A larger number of animals would most certainly have demonstrated significant difference between normals and autografts.

Pulmonary diffusion capacity for carbon monoxide (DLCO) (Fig. 11) following autotransplantation was decreased as compared with the control group. Seven dogs, 32 months after autotransplantation, had a mean left lung DLCO of 6.7 ± 2.8 ml./min./mm Hg. (30% of total DLCO); 16 months later the 6 surviving dogs had a left lung DLCO of 5.7 ± 1.4 ml./min./ mm Hg. This represents the same share (31%) of the total pulmonary diffusion capacity at 48 months as at 32 months. The mean left lung DLCO in the control group was 6.6 ± 3.2 ml./mm Hg. Proportionally, the left normal lung contributed more (40%) to the total diffusion capacity than the autotransplant; however, this difference is not statistically significant because of the large standard deviation in normal left lung DLCO values ($P > 0.1$).

Discussion

It has been known for some time that following autotransplantation the canine lungs show a mild decrease of ventilation and reduction of pulmonary blood flow and oxygen uptake[16,18] These changes have been measured in most instances only a few months after operative procedure. However, Blumenstock, *et al.*, has shown that reimplanted lungs suffer late abnormalities of the ventilation perfusion ratios.[4]

Animals with technical defects of the autografted lung such as stricture of the bronchial or venous anastomoses, are expected to have a reduction of functions. Only one of our dogs had an anatomical defect of the vessels or bronchus that could decrease functional capacity. Some of the other animals had pleural adhesions and fibrosis, and microscopic granulomas of the bronchial anastomosis.

Multiple pulmonary function determinations provide a better idea of the functional capacity of the organ than a single test. Pulmonary function testing is more difficult in animals than in humans because of the lack of cooperation. Bronchospirometric separation of the function of each lung is also essential for a precise evaluation. With the use of a negative pressure box ventilator, we were able to simulate normal respiratory conditions. Without the use of the ventilator, we found great difficulty in obtaining reproducible measurements of compliance. The level of ventilation is rarely steady in dogs under general anesthesia, and continual changes in tidal volume and respiratory rate resulted in measuring compliance at different pulmonary pressures. This problem was obviated by paralyzing the dog and ventilating him steadily with the box respirator, using the same transpulmonary pressure for each test; this arrangement also controlled tidal volume and frequency. These conditions could be repeated any time that pulmonary mechanics were measured. Therefore, any change of compliance could be related to changes in the lung parenchyma.

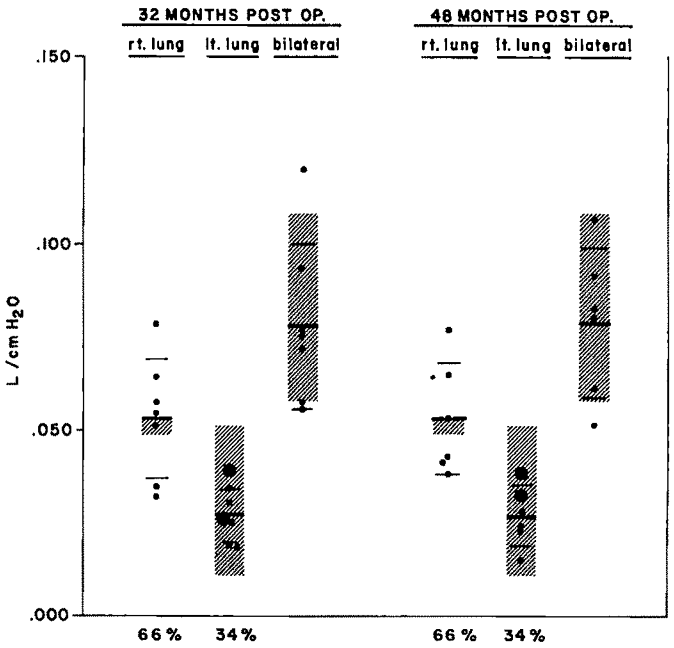

FIG. 9. The compliance of each lung and the bilateral measured value.

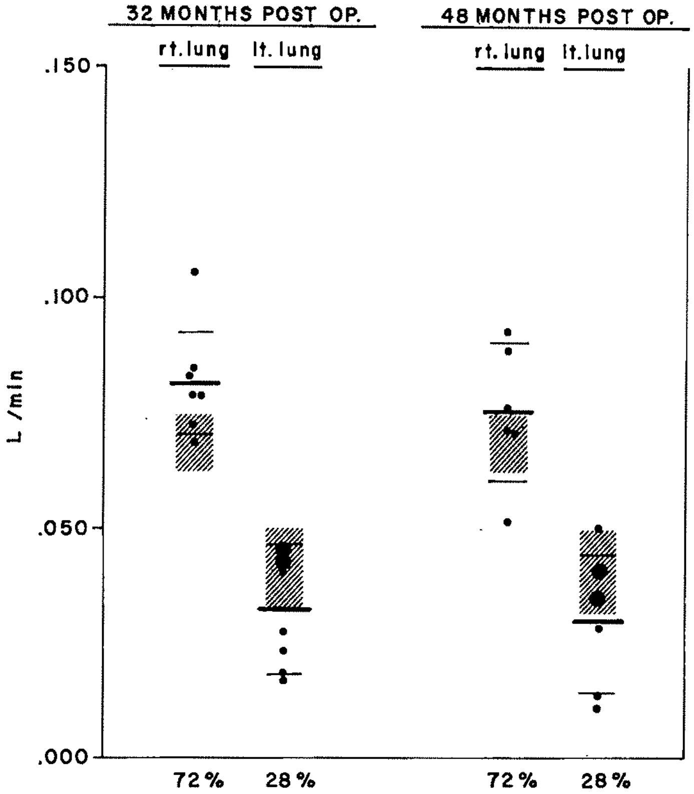

FIG. 10. The oxygen uptake at 32 and 48 months after autotransplantation.

Ideally, pulmonary functions should have been measured before the autotransplantation. However, 4 years ago we were not equipped, nor were we experienced enough to perform these tests. To obtain control data on normal dogs, we tested a group of 6 normal dogs of similar size under the same respiratory conditions, using identical techniques. As can be seen by the standard deviations, compliance, lung volume and diffusion capacity of the left lung are rather variable in normal dogs. This variability has been reported by several authors who performed differential diffusion capacity in normal dogs.[7,11] Because, for technical reasons, the left lung is more commonly autotransplanted, it seems advisable that all future attempts to evaluate the effect of transplantation should include the performance of pulmonary function preoperatively.

Two of the 6 dogs survived contralateral pneumonectomy. Both had better pulmonary function than the rest and their left lungs seem to have been larger than average. Perhaps it is coincidental, but this percentage of survival is the same as reported for left lung autotransplantation with immediate ligation of the contralateral pulmonary artery.[9] Also, we found that one in every 3 normal animals has about the same function in the left lung as in the right. This suggests that dogs which survive with only the left autotransplant lung are those with unusually large functional capacity. If this is true, the reported survivors of that type of preparation will represent a highly selected group of animals. This hypothesis should be confirmed by performing pulmonary function studies before autotransplanting the left lung and ligating the contralateral pulmonary artery.

The mechanical properties of the lung were not significantly changed by the autotransplantation procedure. However, there is some decrease in the total lung capacity and functional reserve capacity of the transplanted lung. A minimal reduction of the left lung compliance was also observed. These restrictions may be caused by the pleural fibrosis and adhesions in most of the specimens and could be the results of the trauma inflicted by the surgical procedure itself. Birch, *et al.*, measured compliance before and shortly after (4–6 weeks) transplanatation. They could not find significant changes brought about by the procedure.[3] Our late measurements indicate that compliance remains unchanged for a period of 4 years.

The reduction of the oxygen uptake of the autotransplanted lung probably was due to a decreased perfusion of the left lung. Published studies with radioactive Xenon[133] indicate abnormal ventilation-perfusion ratio in the autotransplanted lung.[19] An indirect confirmation is found in the increased pulmonary vascular resistance seen in the autotransplanted lung that will direct the flow to the contralateral side. There is probably some reduction of the vascular bed of the autotransplanted lung, but the decrease of $\dot{V}O_2$ was not statistically significant in our group.

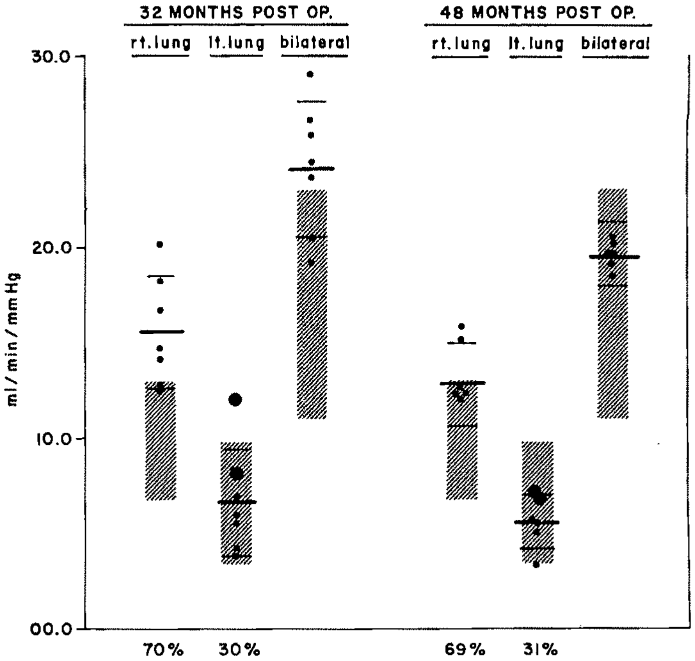

FIG. 11. The pulmonary diffusion capacity for CO of the autografted (left) normal lung, and bilateral at 32 and 48 months postoperatively.

Diffusion capacity was diminished in the transplanted lung as compared with normal dogs, but the total pulmonary diffusion was unchanged. The normal lung took a larger share of the diffusion. Diffusion capacity for CO is not influenced by the pulmonary blood flow, but is dependent upon the area of the alveolar membrane and the distance that the gas travels from the alveoli to the capillary vessel, or in other words, on the thickness of the "alvelocapillary membrane." Our measurement of the total lung volume indicates that the surface of the lung is moderately decreased. This reduction of the area may account for the decreased pulmonary diffusion capacity. Microscopic examination of the lung parenchyma failed to demonstrate increased thickness of the alveolar membrane, although small quantities of interstitial edema may have been present and not detected by light microscopy. The only report that we are aware of measuring DLCO in autotransplanted lungs indicates normal diffusion capacity; however, the 3 dogs included in the study had partial obstruction of the pulmonary venous return, with engorged vessels, a factor that will tend to increase DLCO. Therefore, we cannot make meaningful comparison between our results and those reported.[6]

The total pulmonary vascular resistance 18 months postoperatively was increased in the autotransplanted lung as compared with normal dogs. Following pneumonectomy all the animals showed a considerable increase in the pulmonary artery pressure. However, the rise of PA pressures was not correlated with survival. These hemodynamic changes were not due to pulmonary artery anastomotic stricture or venous narrowing as suggested by others[2,17] Apparently, pulmonary artery pressure increased with time in the autograft. It was within normal limits 16 months following the procedure, but was unequivocally elevated 4 years after the transplantation. In 2 animals, thickening of the intima of peripheral pulmonary arteries may have been responsible for reducing the lumen of the vessels.

Summary

Pulmonary function and hemodynamic studies were performed in a group of dogs up to four years following autografting of the left lung. Lung compliance was unchanged by the surgical procedure. The total lung capacity (T.L.C.) and the functional reserve capacity (F.R.C.) were slightly reduced. The relationship between the T.L.C. and F.R.C., however, was normal There was a reduction of the diffusion capacity and the oxygen uptake in the autografted lung, but these changes were not statistically significant.

Pulmonary arterial pressures and vascular resistance 16 months after autotransplantation were within normal limits, however, 32 months later there was a noticeable increase of the pulmonary pressure of the autografted lung. No evidence of arterial or venous narrowing were found at the anastomotic sites that could explain the above findings. In 2 animals, thickening of peripheral pulmonary arterial walls may have been responsible for the increased pressure. A third of the animals survived contralateral pneumonectomy.

References

1. Bergan, F.: The Investigation of the Relative Function of the Sight and Left Lung by Bronchospirometry. New York and London, Grune and Stratton, Inc., 1951.
2. Benfield, L. R., Coon, R.: The Role of the Left Atrial Anastomosis in Pulmonary Reimplantation. J. Thor. Cardiovasc. Surg., 53:676, 1967.
3. Birch, A. A., Secrist, W. L., Becker, M. K., Trummer, M. J.: Pulmonary Functions Before and After Lt. Lung Autotransplantation. Arch. Surg., 97:1968.
4. Blumenstock, D. A., Lempert, N., Singer, K. M., Kasemi, H., Fenneba, J. W.: Late Pulmonary Function After Reimplantation and Allotransplantation of the lung in Dogs. Transplantation, 10:241, 1970.
5. Bouma, H. G. D., ten Hoor, F., Scherpenisse, L. A., Kleine, J. W., Ovie, N. G., Homan van der Heide, J. N.: Long-term Observation of the Changes in Pulmonary Artery Pressure After Reimplantation of the Caine Lung. J. Thor. Cardiovasc. Surg., 56:799, 1968.
6. Brody, T. S., Fisher, A. B., Park, C. D., Hyde, R. W., Waldhausen, J. A.: Factors Influencing Function of the Autotransplanted Lung. J. Appl. Physiol., 29:587, 1970.
7. Cree, W. M., Benfield, J. R., Rasmussen, H. K.: Differential Lung Diffusion, Capillary Volume and Compliance in Dogs. J. Appl. Physiol., 25:186, 1968.
8. Diacoff, G. R., Allen, P. D., Streck, C. J.: Pulmonary Vascular Resistance Following Lung Reimplantation and Transplantation. Ann. Thorac. Surg., 9:569, 1970.
9. Ebert, P. A., Hudson, B. H.: Pulmonary Hemodynamics Following Lung Autotransplantation. J. Thor. Cardiovasc. Surg., 62:188, 1971.
10. Garzon, A. A., Cheng, C., Pangan, L., Karlson, K. E.: Hypothermic Hyperbaric Lung Preservation for Twenty-four Hours with Replantation. J. Thor. Cardiovasc. Surg., 55:546, 1938.
11. Glauser, E. M.: Differential Pulmonary Diffusion Capacity in Normal Dogs. J. Appl. Physiol., 22:109, 1967.
12. Kleinman, L. I., Radford, Jr., E. P.: Ventilation Standards for Small Mammals. J. Appl. Physiol., 19:360, 1964.
13. Marshall, R., Gunning, A. J.: The Long-term Physiological Effect of Lung Reimplantation in the Dog. J. Surg. Res., 6:185, 1966.
14. Mead, L., Collier, C. R.: Relation of Volume History of Lung to Respiratory Mechanics in Anesthetized Dogs. J. Appl. Physiol., 14:669, 1959.
15. Ogilvie, C. M., Forster, R. E., Blackmore, W. S., Morton, L. W.: A Standardized Breath Holding Technique for the Clinical Measurement of the Diffusing Capacity of the Lung for Carbon Monoxide. J. Clin. Invest., 36:1, 1957.
16. Suzuki, C., Nakata, T., Moriyama, R., Kukimura, S.: Functional Studies of the Transplanted Lung. J. Thor. Cardiovasc. Surg., 57:562, 1969.
17. Veith, F. L., Richard, K.: Mechanism and Prevention of Fixed High Vascular Resistance in Autografted and Allografted Lungs. Science, 163:699, 1969.
18. Waldhausen, L. A., Daly, W. J., Baez, M., Giammoma, S. T.: Physiologic Changes Associated with Autotransplantation of the Lung. Ann. Surg., 165:580, 1967.
19. Yeh, T. J., Ellison, L. J., Ellison, R. G.: Function Evaluation of the Autografted Lung in Dogs. Am. Rev. Resp. Dis., 86:791, 1962.

Mechanism of Microaggregate Formation in Stored Blood

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BLOOD STORED at 4° C. in ACD solution has been shown to develop microaggregates composed primarily of platelets and fibrin.[7,10] This debris in transfused blood has been shown to produce changes in pulmonary hemodynamics in animals[3,6] and has been implicated in the pathogenesis of post-traumatic pulmonary insufficiency in man.[4,8,9]

The present studies were undertaken to define more clearly the mechanism by which these microaggregates are formed. It is directed primarily at studying evolutionary changes in platelet function and fibrinogen composition of stored human blood.

Materials and Methods

Ten units of fresh human blood were collected in the customary fashion in plastic bags containing ACD solution and stored at 4° C. Blood was studied on the day of collection, each subsequent day for 5 days and at 3-day intervals thereafter.

Studies included the following:

Hematocrit (microhematocrit method)

Platelet Count (phase contrast microscopy)

Platelet Aggregation (percentage decrease in optical density 4 minutes after addition of 0.1 uM· ADP solution)[2]

Screen Filtration Pressure (both quantitative and qualitative as previously described)[5]

Serum Fibrinogen[12]

Fibrinogen content of microaggregate material. This was performed by adding 25 ugm of ^{125}I tagged 90% clottable human fibrinogen to each bag of freshly drawn blood. Blood was counted before filtration through the SFP apparatus with a Scintillation counter. The SFP and debris weight was then determined. The SFP screen was removed, weighed and counted and the filtrate volume was measured and counted. Fibrin on the serum was expressed as counts/gm of debris.

Results

Hematocrit remained quite stable throughout the 21 days of storage (Fig. 1). Platelet count rose initially, then fell progressively from 2 through 15 days, remaining constant for the remaining 6 days of study (Fig. 2). Platelet aggregation increased slightly during the first 3 days of storage, stabilized through day 10 and fell during the remainder of the storage period (Fig. 3). Debris accumulation began at day 2 and increased to day 5, remained constant through day 10, then increased rapidly during the next 11 days of storage (Fig. 4). Scintillation counts remained constant during the first 10 days of storage, then increased rapidly, paralleling the increase in debris weight for the remainder of the storage period (Fig. 5).

Discussion

The small but significant initial rise in platelet count may be explained by de-aggregation of small platelet aggregates formed during the process of blood drawing. Increase in platelet propensity to aggregate parallels the early formation of microaggregates detected by SFP from storage days 2 through 5. Platelet count and aggregation remained stable from days 4 through 10. At the same time, no further microaggregate accumulation was noted suggesting that the initial microaggregate formation was due primarily to platelets. This is further sup-

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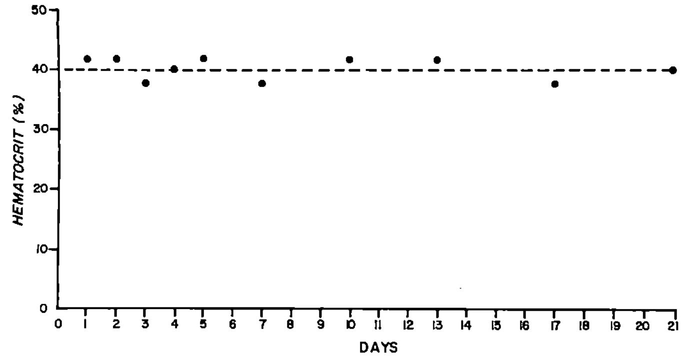

FIG. 1. Hematocrit through 21 days of storage.

ported by the relative paucity of ^{125}I fibrinogen on the screens during these first 10 days. It is likely that significant platelet function has disappeared by day 4. The continued response of platelet to ADP during this period is difficult to explain but suggests some residual ability of non-viable platelets to respond to ADP. Platelet viability is generally absent beyond 3 or 4 days of storage so that the observed response does not suggest normal platelet function beyond 4 days. The fact that no further microaggregates from beyond 4 days implies absence of platelet function and is consistent with published observations on platelet viability.[1,11] The exact nature of the observed response of platelets, stored beyond 4 days, to ADP remains obscure.

Studies with ^{125}I tagged fibrinogen indicate that until 10 days, fibrin contributes little to the microaggregate bulk. Beyond 10 days, however, SFP weight increases rapidly, paralleled by an increase in ^{125}I counts on the screen.

It, therefore, appears that microaggregates form in stored blood after 2 days of storage, primarily as a consequence of platelet aggregation. Furthermore, most of the matetrial is composed of platelets. From 4 to 10 days of storage, little change occurs in the amount of microaggregates in the blood. At about 10 days, however, fibrin begins to accumulate progressively on pre-existing platelet aggregates resulting in a progressive increase in the mass of microaggregates in the blood. This implies that the actual number of particles do not increase after the first 4 or 5 days of storage, but that further increase of microaggregate mass is due to deposition of fibrin on pre-existing platelet aggregates.

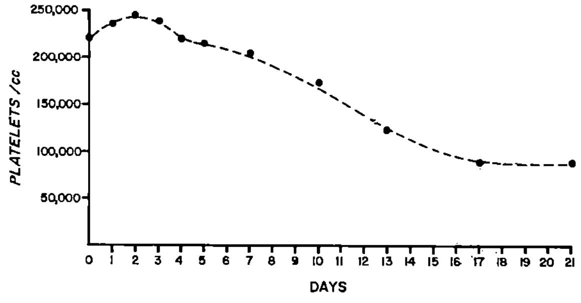

FIG. 2. Platelet count.

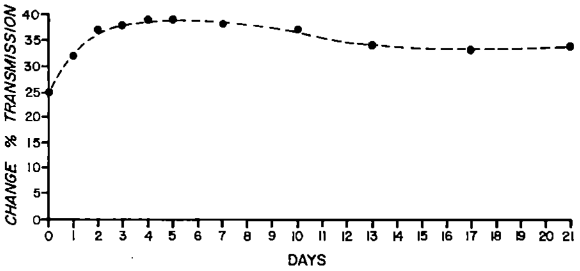

FIG. 3. Platelet aggregation response to ADP.

Microaggregates have been previously implicated in the pathogenesis of post-traumatic pulmonary insufficiency. It is not known whether platelet aggregates alone will produce pulmonary microemboli of any physiologic significance. It is conceivable that the risk of pulmonary damage is considerably greater with larger microemboli composed of both platelets and fibrin. If the latter is the case, then use of banked blood stored less than 10 days would circumvent the problem. On the other hand, if small microaggregate emboli composed primarily of platelets can produce pulmonary damage, then prevention of such early microaggregate formation and/or more effective filtration of all blood stored for over 2 days should be considered. Further investigation is currently underway to answer these questions.

Summary

Banked blood, collected in ACD solution and stored at 4° C., develops microaggregates which form during the second to the fifth day of storage. Microaggregate formation is accompanied by a transient increase in platelet aggregation to ADP and suggests that these are principally platelet aggregates. Microaggregate weight remains

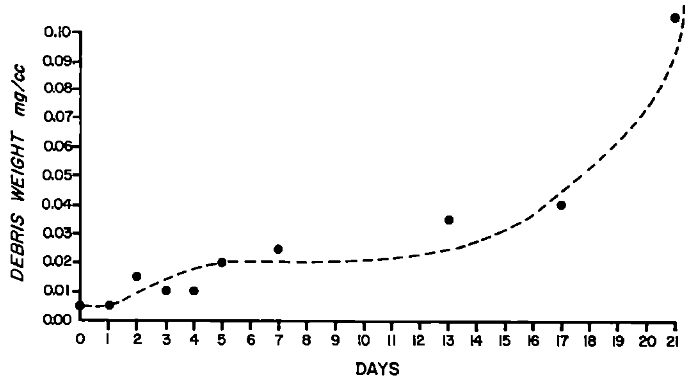

FIG. 4. Debris accumulation.

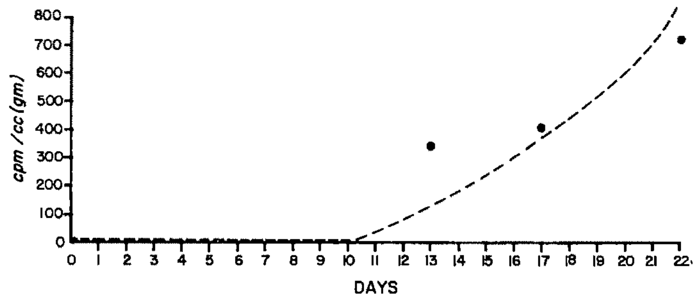

FIG. 5. ^{125}I fibrogen cpm/cc (gm) corrected to day 0 counts.

stable until 10 days beyond which a progressive increase is noted. Studies with ^{125}I tagged fibrinogen suggest that this increase beyond 10 days is due primarily to accumulation of fibrin on previously formed platelet aggregates.

References

1. Cohen, P., Gardner, F. and Barnett O.: Reclassification of the Thrombocytopenias by the Cr^{51}-labeling Method for Measuring Platelet Life Span. New Engl. J. Med., **264**:1350, 1961.
2. Goldenfarb, P. B., Cathey, M. H. and Cooper, G. R.: The Determination of ADP-induced Platelet Aggregation in Normal men. Atherosclerosis, **12**:335, 1970.
3. Hissen, W. and Swank, R. L.: Screen Filtration Pressure and Pulmonary Hypertension. Am. J. Physiol., **209**:715, 1965.
4. Jenevein, E. P., and Weiss, D. L.: Platelet Microemboli Associated with Massive Blood Transfusion. Am. J. Path., **45**:313, 1964.
5. McNamara, J. J.: Effective Filtration of Banked Blood. Surgery, **71**:594, 1972.
6. McNamara, J. J., Burran, E. L., Larsen, E., Omiya, G., Suehiro, G., and Yamase, H.: Effect of Debris in Stored Blood on Pulmonary Microvasculature. Ann. Thorac. Surg., **14**: 133, 1972.
7. McNamara, J. J., Molot, M. D. and Stremple, J.: Changes in Some Physical Properties of Stored Blood. Ann. Surg. **174**:58, 1971.
8. McNamara, J. J., Molot, M. D. and Stremple, J. F.: Screen Filtration Pressure in Combat Casualties. Ann. Surg., **172**: 334, 1970.
9. Moore, F. D., *et al.*: Post-traumatic Pulmonary Insufficiency. Philadelphia, W. B. Saunders Co., 157, 1969.
10. Swank, R. L.: Alterations of Blood on Storage: Measurement of Aging Platelets and Leukocytes and their Removal by Filtration. New Engl. J. Med. **265**:728, 1961.
11. Tranum, B. L. and Haut A.: In vivo Survival of Platelets Prepared in CPD Anticoagulant. Transfusion, **12**:168, 1972.
12. Ware, A., Guest, M. M. and Seegers, W. H.: Fibrinogen: With Special Reference to its Preparation and Certain Prospectives of the Product. Arch. Biochem., **13**:231, 1947.

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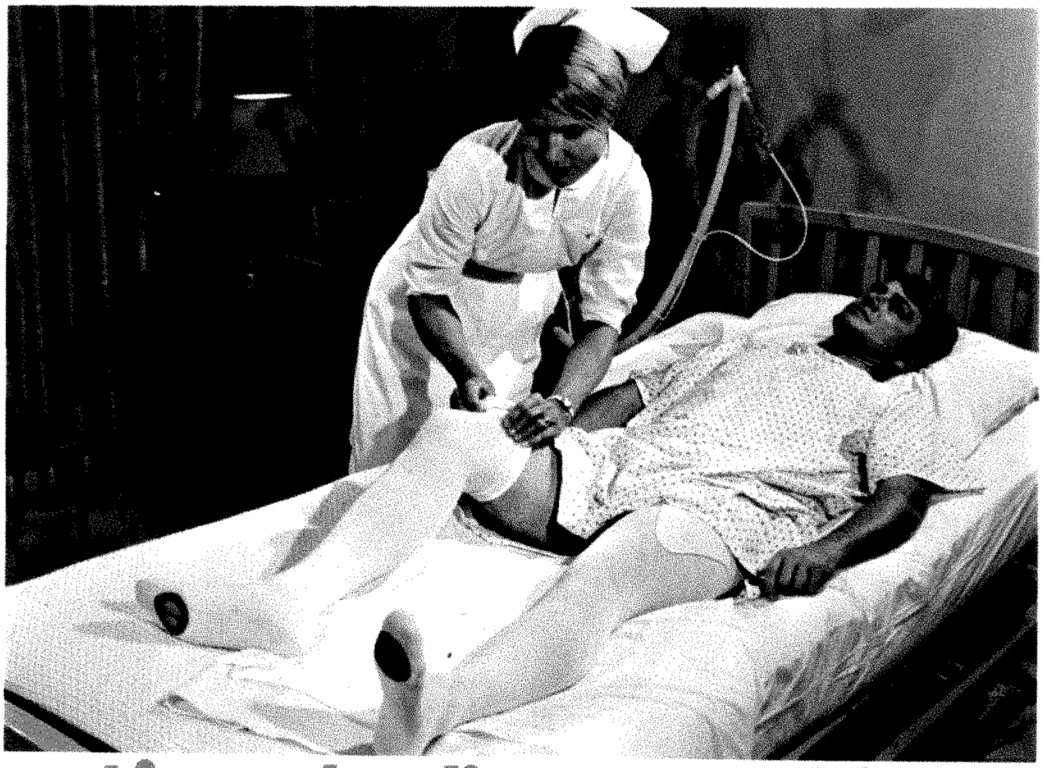

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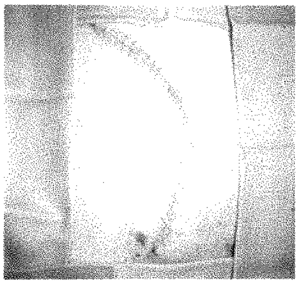
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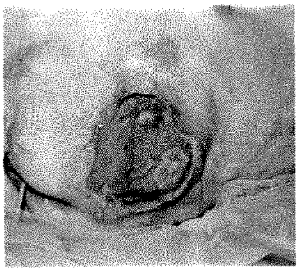
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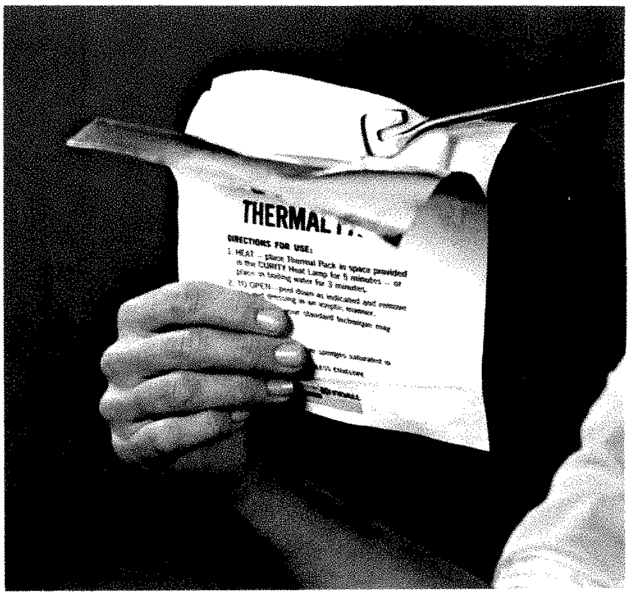

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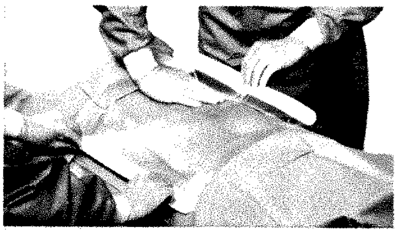

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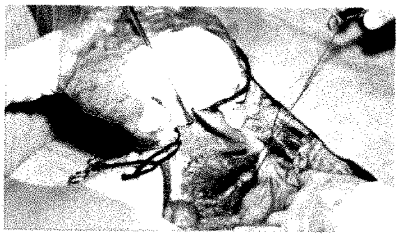

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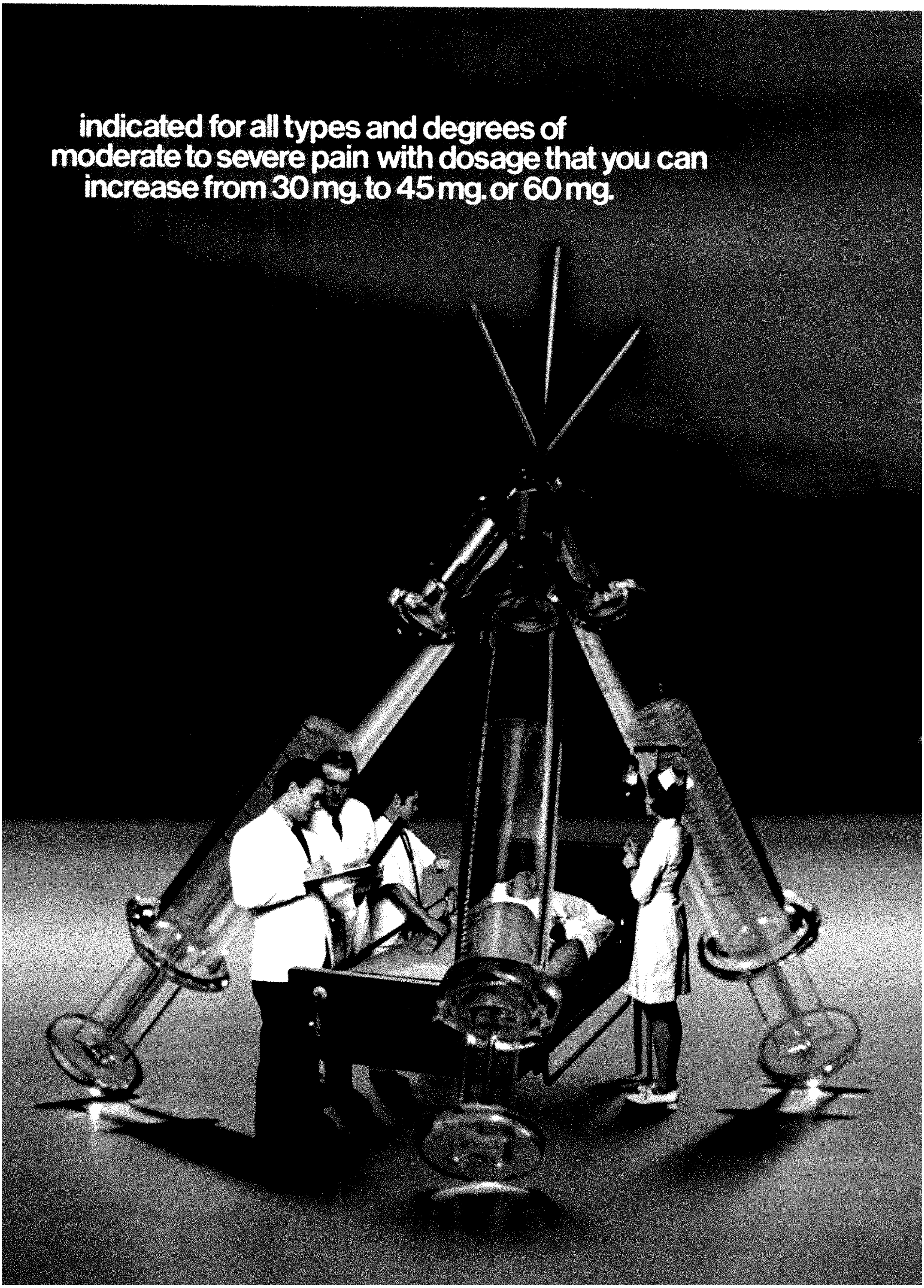

indicated for all types and degrees of
moderate to severe pain with dosage that you can
increase from 30 mg. to 45 mg. or 60 mg.

An analgesic as potent as you need

Type of pain	Dosage	No. patients studied	Incidence of excellent to good analgesia	Adverse Reactions
post-operative pain[1]*	**30 mg.**	29	79.3%	"As the study progressed, the dosage was increased to 45 and 60 mg. to determine whether higher doses would produce greater analgesia without an increase in adverse effects."[1]
	45 mg.	70	83.0%	"Only a few minor side effects were observed."[1]
	60 mg.	101	94.0%	
post-operative pain[2]†	**30 mg. or 60 mg.**	68	94.0%	"At the start of the study, adult patients were given 30 mg. doses. It was found, however, that a 60 mg. dose gave better analgesia with no noticeable difference in tolerance."[2]

*Study based on response to a single dose.

†Study based on multiple doses, according to patient need.

References: 1. Finestone, S. C. and Katz, J.: Pentazocine as a postoperative analgesic, *Anesth. Analg.* 45:312, May-June 1966. 2. Snow, E. W.: Pentazocine—clinical evaluation, *Abdom. Surg.* 9:150, May 1967.

Provides relief comparable to that of morphine and meperidine, but with fewer significant adverse effects††

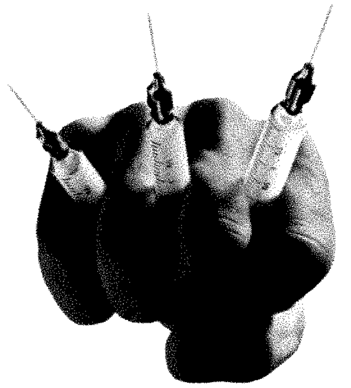
- Compared to morphine, Talwin causes less severe respiratory depression, hypotension, urinary retention, constipation.
- Compared to meperidine, Talwin is less likely to cause nausea, vomiting, diaphoresis.

††See next page for a complete discussion of Warnings, Precautions, Adverse Reactions, and other Prescribing Information.

Injectable

Talwin® brand of pentazocine (as lactate)

30 mg. 45 mg. 60 mg.



Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, soft tissue induration, nodules, cutaneous depression, and ulceration (sloughing) at the injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.)* in boxes of 25. Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

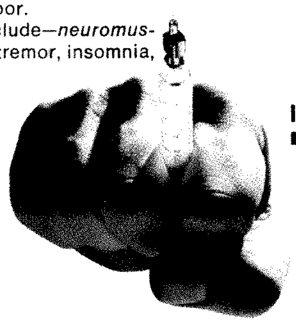
Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

Winthrop

bulwark against pain
of moderate to severe intensity



Injectable
Talwin®
brand of
pentazocine
(as lactate)

(1617)

Sound Surgery:

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Push-button surgery is here! Taped conferences make catching up on recent surgical advances as easy as pushing a button on your cassette player. Drs. John Delaney and Richard Varco host guest experts on a variety of surgical topics. January's inaugural issue features John Goligher on *Crohn's Disease* and Paul Ebert on *Pulmonary Embolism.* Upcoming tapes will focus on *breast lumps, retained calculi in the common duct, carcinoma of the colon, diffuse gastric mucosal bleeding,* and *intestinal fistulas and anastomoses.* Published every other month on C-60 cassettes. $52.50 per year. **Order # 0033.**

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Published quarterly, the Orthopedic Clinics combine the depth and permanence of a textbook with the frequency and timeliness of a periodical—a must for specialists. 1974's issues will include symposia on *Proceeding of the American Orthopaedic Foot Society, Tendon Transfers in the Upper Extremity,* and *The Shoulder.* About 225 pp. per issue. No advt. $30.00 per year. **Order # 0004.**

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Scheduled 1974 symposia in this hard-hitting periodical are of special interest to surgical specialists: *Revision Surgery in Otorhinolaryngology* in February and *Disease and Injury of the Facial Nerve* in June. (October not yet scheduled.) About 200 pp. per issue. No advt. $22.00 per year. **Order # 0005.**

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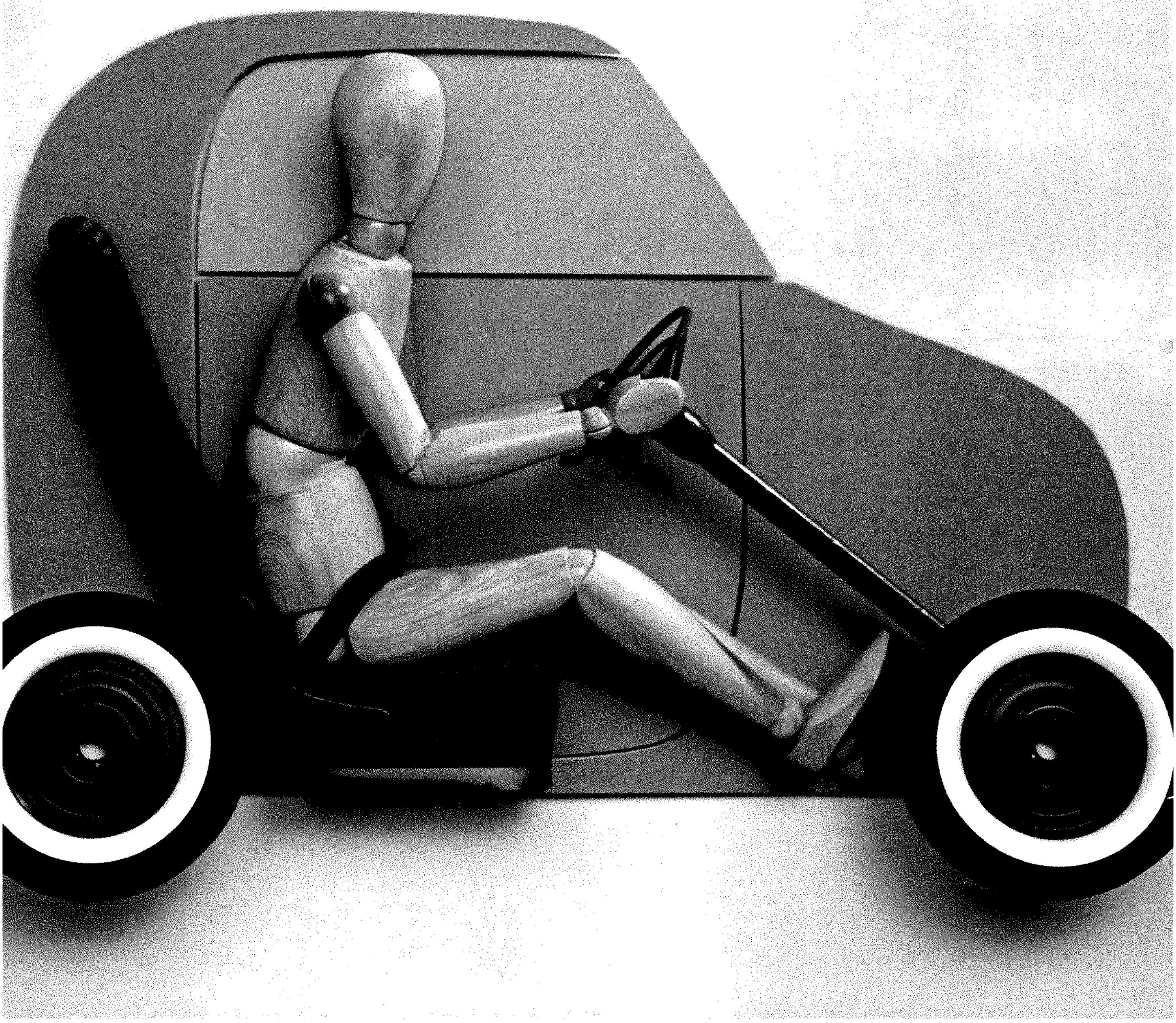
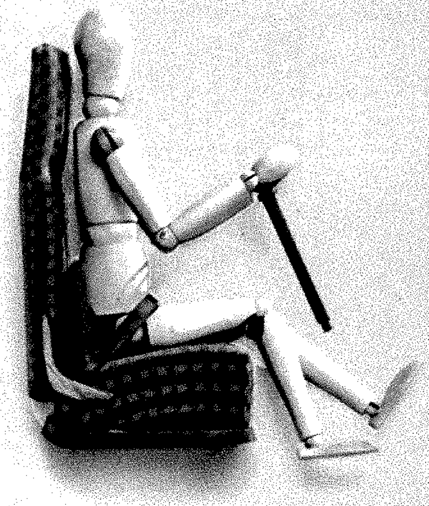
the low-back patient and his problems:

DRIVER'S BACKACHE

Neck and shoulders rigid and tense
Upper back strained forward
Lower spine slumped
Soft seat can't support vertebrae and low-back muscles
Left leg "frozen" in cramped position
Right leg stretched to reach gas and brake pedals



the solution:



Push front seat forward to reduce strain on back and shoulder muscles. Insert small cushion between small of back and rear of car seat. Back support can help relieve pain and fatigue. Always wear seat belt and shoulder harness. On long trips get out of car and stretch every couple of hours.

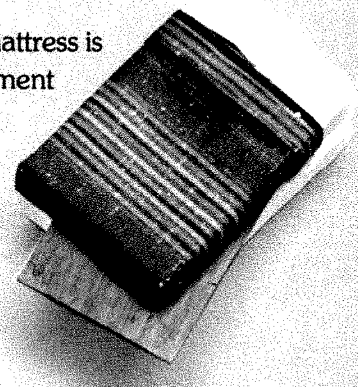
to treat acute musculoskeletal disorders…

ROBAXIN®-750

(methocarbamol) 750 mg. capsule-shaped tablets

the Robaxin® Regimen:

Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort. Have patient insert section of plywood ½-¾" thick between mattress and box springs. The use of moist heat is often very beneficial.



To relieve the discomforts associated with acute musculo-skeletal disorders, Robaxin®-750 is often indicated.* It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

* **Indications**
Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: Relief of discomforts associated with acute musculoskeletal disorders.
Final classification of the less-than-effective indications requires further investigation.

Contraindications:
Methocarbamol is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effect upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Adverse Reactions:
Light-headedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:
NOTE: Because of limited clinical experience in the younger age group, Robaxin is not recommended for use in patients under 12 years of age except in tetanus.

Adults:
Initial dosage, 2 tablets q.i.d. Maintenance dosage, 1 tablet q. 4h. or 2 tablets t.i.d.

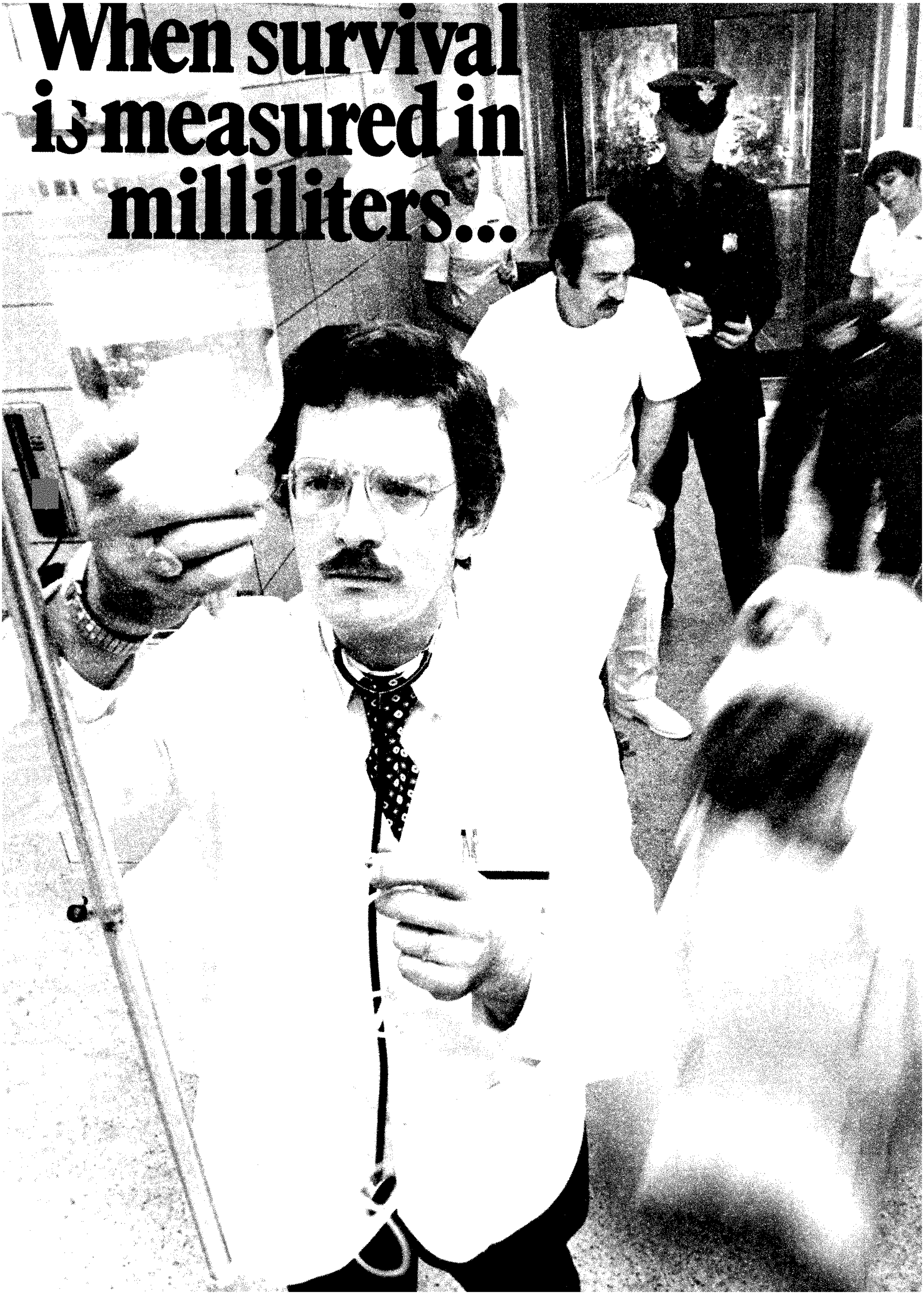
Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

Also Available:
ROBAXIN® (methocarbamol) 500 mg.

See package insert for full prescribing information.

A.H. Robins Company, 1407 Cummings Drive, Richmond, Va. 23220
A·H·ROBINS

Rx 74000-56 1974


When survival is measured in milliliters...

Moments and milliliters... both are critical in treating hypovolemic shock since survival depends on the rapid, efficient restoration of circulating blood volume. Also crucial is the volume expander you use "stat." Rheomacrodex starts to work immediately to restore blood volume and adequate tissue perfusion.

Greater Initial Plasma Volume

In a recent study,[1] plasma volume expansion and cardiac output were measured in 36 patients with moderate or severe degrees of shock and in eight healthy subjects before, during and after infusion with 500 ml 10% dextran 40, whole blood, 6% dextran 70, plasma, and 5% dextran 40. The greatest plasma volume expansion was established in the 24 shock patients treated with Rheomacrodex. Peak plasma volume increases were more than one liter above controls. Plasma volumes decreased slowly as urinary output increased. Other studies also show the superiority of Rheomacrodex over blood, plasma, saline or lactated Ringer's for increasing initial plasma volume.[2-5]

Improved Cardiac Output

Measurement of hemodynamic effect revealed increased cardiac output directly related to increased volume expansion. Peak C.O. values occurred 15 minutes after Rheomacrodex infusion. In patients with moderate or severe degrees of shock, 10% dextran 40 increased cardiac output an average of 70% above control values.[1] Rheomacrodex improves hemodynamics – restores effective cardiac output and tissue perfusion – better than whole blood, plasma or clinical dextran.

Increased Tissue Perfusion

Restoring blood pressure often is not enough to reverse shock. Most important is the maintenance of adequate tissue perfusion. Rheomacrodex achieves this by decreasing red blood cell aggregation to a greater extent than crystalloids, blood or plasma.[6-10] This improvement in microcirculatory blood flow is reflected in increased oxygen availability and consumption, a vital contribution to the reversal of shock.[11]

Delayed Renal Excretion

In hypovolemia, delayed renal clearance tends to prolong the colloid osmotic effects of Rheomacrodex.[1] During infusion, Rheomacrodex is evenly distributed in the vascular system. The plasma concentration of dextran falls rapidly during the first hour as smaller molecules are excreted. Generally, 70% of Rheomacrodex infused in normovolemic subjects is excreted via the kidney in 24 hours.[12] Excretion is then slowed as the higher molecular weight fraction of dextran remains in the circulation to be metabolized at the rate of 70-90 mg/kg body weight per 24 hours.

Guidelines for Use

1. May be administered on a "response to therapy basis" up to 1,500 ml initially in first 24 hours.
2. Infuse first 500 ml within 30 minutes.
3. To support blood volume beyond 24 hours, administer 500 to 1,000 ml daily.
4. Do not continue beyond five days.
5. May be given with whole blood.
6. Keep patient well hydrated. Increase hydration if urine flow drops below 50 ml/hour.
7. Can be given to any patient without blood typing. However, blood should be drawn prior to infusion for future testing.

REFERENCES: 1. Shoemaker, W.C. and Monson, D.O.: Surg. Gynec. Obstet. 137:453, 1973. **2.** Ahnefeld, F.W. et al.: Anaesthesist 14:137 (May) 1965. **3.** Gelin, L.E. et al.: Acta Chir. Scand. 122:309, 1961. **4.** Gruber, U.F. et al.: Proc 10th Cong Int Soc Blood Transf., 1965, pp. 1116-1119, S. Karger, Basel (Switzerland). **5.** Gruber, U.F. et al.: Symposium on Rheomacrodex I (1964), pp. 13-23. **6.** Mainardi, L.C. et al.: Surgery 56:349 (Aug.) 1964. **7.** Martinovic, N. and Melrose, D.: J. Cardiovasc. Surg. 4:610 (Aug.) 1963. **8.** Suzuki, F. et al.: Ann. Surg. 160-263 (Aug.) 1964. **9.** Baker, R.J. et al.: Arch. Surg. 90:538 (Apr.) 1965. **10.** Baker, R.J. et al.: Arch. Surg. 89:373 (Aug.) 1964. **11.** Mohr, P.A. et al.: Circulation 39:379 (1969). **12.** Arturson, G. and Wallenius, G.: Scand. J. Clin. Lab. Invest. 16:81, 1964.

Rheomacrodex®

(dextran 40)

For greater blood volume...faster

CONTRAINDICATIONS: Hypersensitivity to dextran. Marked hemostatic defects of all types. Marked cardiac decompensation. Renal disease with severe oliguria or anuria.

WARNINGS: Severe and fatal anaphylactoid reactions may occur infrequently during the early part of the first infusion of dextran. If such reactions appear imminent, stop infusion immediately. Since dextran draws water from extravascular space, give dehydrated patients additional fluids (degree of dehydration can be assessed by serum or urine osmolarity). Diuretics may be used to maintain adequate urine flow. Renal failure, sometimes irreversible, osmotic nephrosis, and, occasionally, abnormal hepatic and renal function values have been reported. Because safety in early pregnancy has not been established, do not use in women of childbearing age unless potential benefits outweigh risks. Use cautiously in patients with active bleeding.

PRECAUTIONS: Doses up to 15 ml/kg may produce small changes in coagulation; factor VIII may decrease markedly, but bleeding time is only rarely prolonged significantly. Observe all patients for early signs of bleeding complications. Monitoring of central venous pressure may help avoid circulatory overloading. Do not depress hematocrit below 30 vol. %. Dextran interference with blood glucose determinations, some blood typing and cross matching procedures and bilirubin and protein assays can be avoided by drawing blood samples prio giving Rheomacrodex or by informing lab that Rheomacrodex has been given so that suitab assay methods can be used.

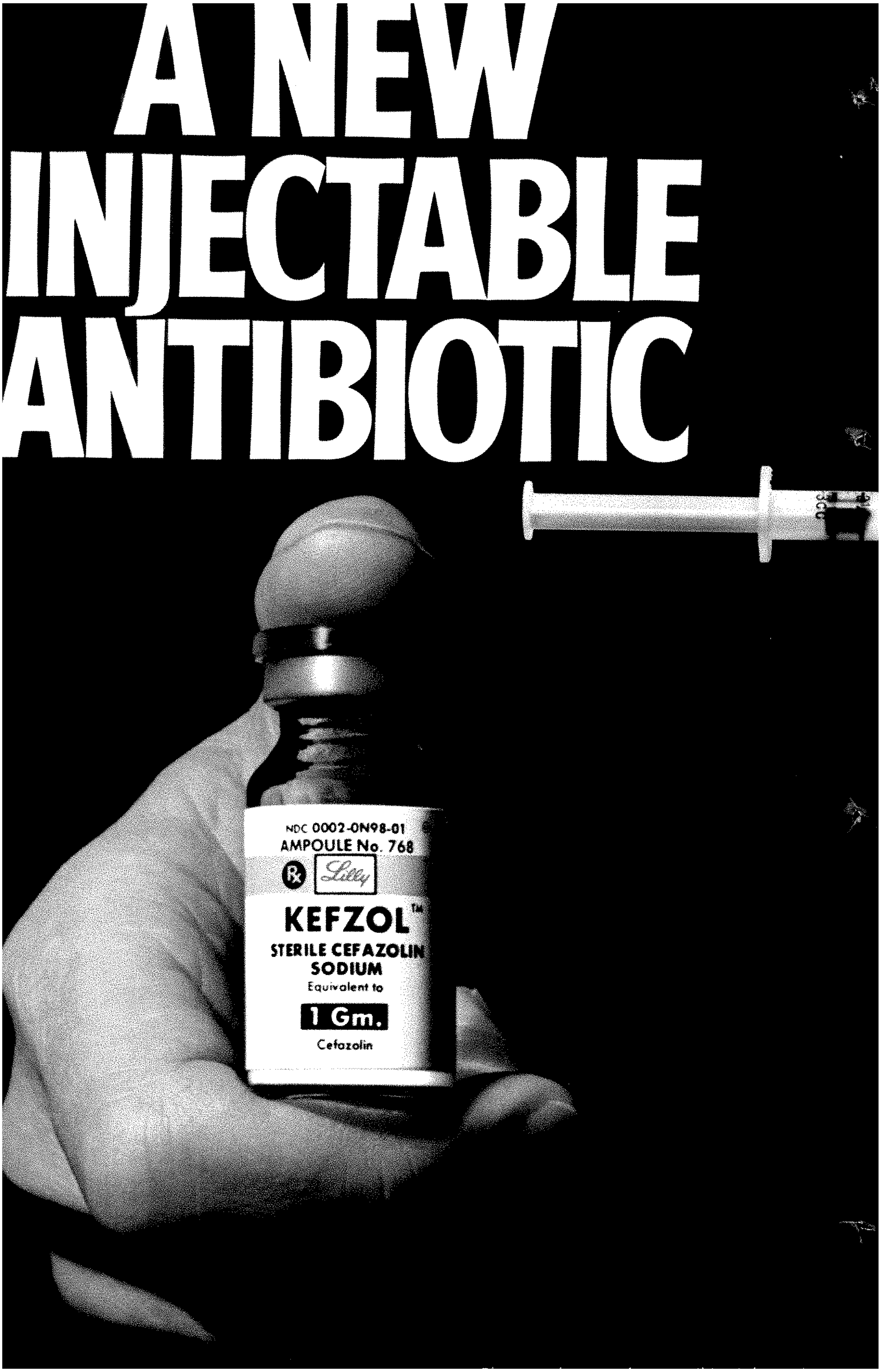
ADVERSE REACTIONS: Hypersensitivity reactions, which occur infrequently, can range fron mild cutaneous eruptions to generalized urticaria, nausea and vomiting, tightness of the ch wheezing, and, rarely, to anaphylactoid (allergic) shock. If any such reactions appear, start appropriate countermeasures promptly.

DOSAGE: Total dosage should not exceed 20 ml/kg in the first 24 hours or 10 ml/kg in eacl subsequent 24 hours. Do not continue beyond 5 days.

SUPPLIED: Bottles of 500 ml 10% solution in normal saline or in 5% aqueous dextrose.

Pharmacia

PHARMACIA LABORATORIES INC.
800 Centennial Avenue, Piscataway, New Jersey 08854



A NEW INJECTABLE ANTIBIOTIC

Lilly
introduces
a new
cephalosporin

Kefzol™

cefazolin sodium

Ampoules, equivalent to 250 mg., 500 mg., and 1 Gm. of cefazolin

Its major areas of indication:

respiratory tract infections

due to susceptible strains of *Diplococcus pneumoniae*, *Klebsiella* species, *Hemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci (Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.)

genito-urinary tract infections

due to susceptible strains of *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, and some strains of *Enterobacter* and enterococci

skin and soft-tissue infections

due to susceptible strains of *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci

See prescribing information for additional indications and susceptible organisms.

Some of its major features:

therapeutic serum levels

peak serum levels of 37.9 and 63.8 mcg./ml. respectively were obtained one to two hours following 500-mg. and 1-Gm. I.M. doses of cefazolin

antibacterial urinary concentrations

peak urine concentrations of approximately 2,400 and 4,000 mcg./ml. respectively were obtained following I.M. doses of 500 mg. and 1 Gm.

bile and synovial-fluid levels

levels approximately one-half those of serum concentrations

flexibility of administration

usual adult dosage—500 mg. to 1 Gm. t.i.d. or q.i.d.

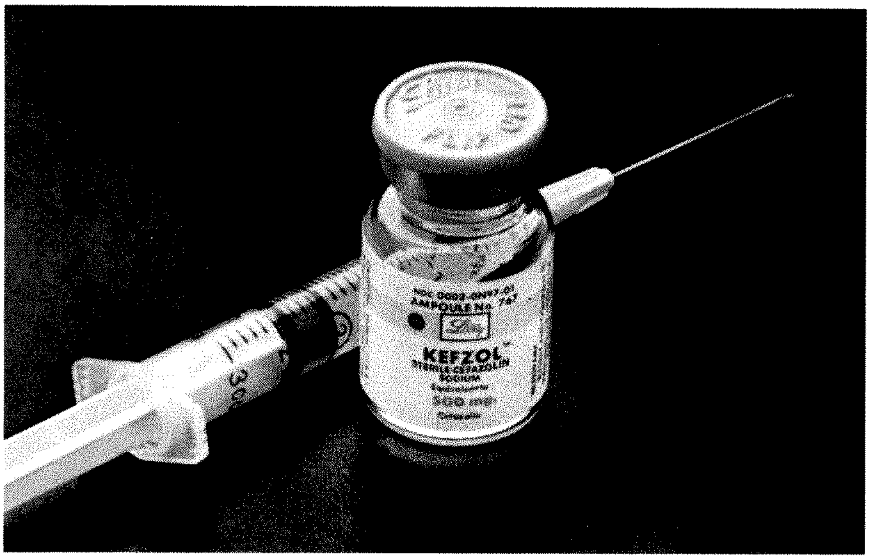
Kefzol is contraindicated in patients with known allergy to cephalosporins and should be given with great caution to penicillin-allergic patients.

Please see following page for summary of prescribing information.

301623

Kefzol™
cefazolin sodium

a new injectable antibiotic



Description: Kefzol™ (cefazolin sodium, Lilly) is a semisynthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl) thio]methyl}-8-oxo7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

Actions: *Microbiology*— In-vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis. Kefzol is active against the following organisms in vitro:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole-positive *Proteus* (*Pr. vulgaris, Pr. morganii, Pr. rettgeri*) are resistant. Methicillin-resistant staphylococci, *Serratia, Pseudomonas, Mima,* and *Herellea* species are almost uniformly resistant to cefazolin.

Indications: Kefzol is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *D. pneumoniae, Klebsiella* species, *H. influenzae, Staph. aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci

Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Kefzol is effective in the eradiction of streptococci from the nasopharynx; however, data establishing the efficacy of Kefzol in the subsequent prevention of rheumatic fever are not available at present.

Genito-urinary tract infections due to *Esch. coli, Pr. mirabilis, Klebsiella* species, and some strains of *Enterobacter* and enterococci

Skin and soft-tissue infections due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci

Bone and joint infections due to *Staph. aureus*

Septicemia due to *D. pneumoniae, Staph. aureus* (penicillin-sensitive and penicillin-resistant), *Pr. mirabilis, Esch. coli,* and *Klebsiella* species

Endocarditis due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Kefzol™ (cefazolin sodium, Lilly).

Contraindication: KEFZOL IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

Warnings: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Kefzol, cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy— Safety of this product for use during pregnancy has not been established.

Usage in Infants— Safety for use in prematures and infants under one month of age has not been established.

Precautions: Prolonged use of Kefzol may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When Kefzol is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false-positive reaction for glucose in the urine of patients on Kefzol has occurred with Clinitest® tablets solution.

Adverse Reactions: The following reactions have been reported:

Hypersensitivity—Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood— Neutropenia, leukopenia, thrombocythemia, and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal—Transient rise in SGOT, SGPT, BUN, and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.

Gastro-Intestinal— Nausea, anorexia, vomiting, diarrhea, and oral candidiasis (oral thrush) have been reported.

Other— Pain at the site of injection after intramuscular administration has occurred, some with induration. Phlebitis at the site of injection has been noted.

Administration and Dosage: Kefzol may be administered intramuscularly or intravenously after reconstitution.

Dosage— In adults, usual dosage for mild gram-positive infections is 250 to 500 mg. of Kefzol every eight hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every eight hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 Gm. of Kefzol every six to eight hours. Kefzol has been administered in dosages of 6 Gm. per day in serious infections such as endocarditis. Kefzol may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.), 60 percent of the normal daily dose given in divided doses q. 12 h. should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.), 25 percent of the normal daily dose given in divided doses q. 12 h. should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.), 10 percent of the normal daily dose given q. 24 h. should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per Kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per Kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of Kefzol in these patients is not recommended.

How Supplied: Ampoules Kefzol™ (cefazolin sodium, Lilly), Sterile, equivalent to 250 or 500 mg. cefazolin, 5-ml. size, rubber-stoppered; equivalent to 1 Gm. cefazolin, 10-ml. size, rubber-stoppered.

[102473]

Lilly

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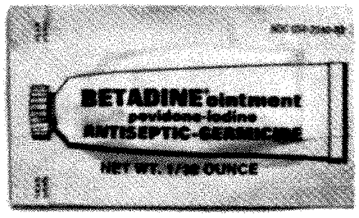
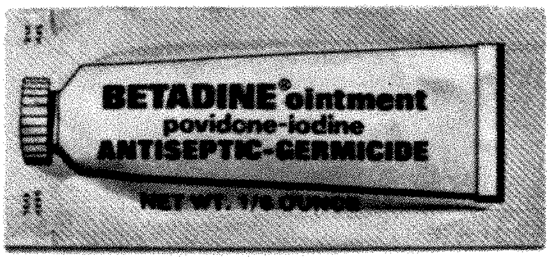
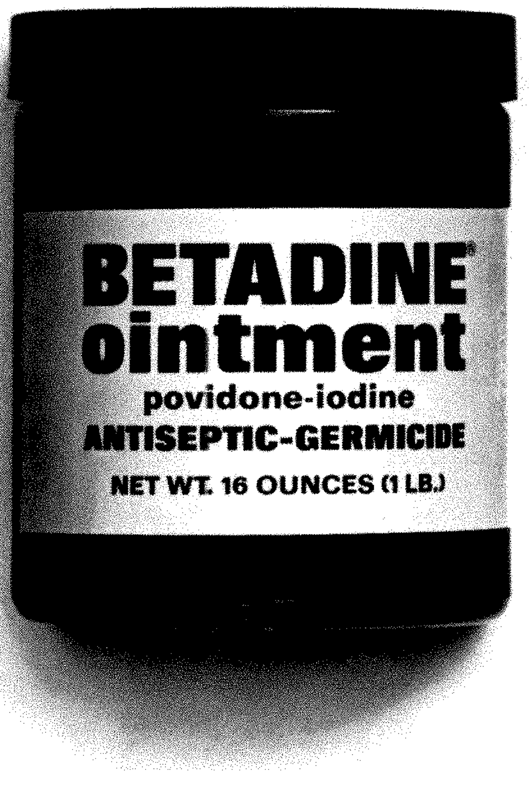


Packette 1/32 oz.
Single-use size for degerming small skin areas, as in the case of umbilical cord care and circumcision.



Packette 1/8 oz.
Single-use size for degerming small skin areas, as in the case of hyperalimentation and catheter care.

Tube 1 oz.
Multiple-use size for treating common skin infections . . . preventing infection in lacerations, abrasions and burns.



Jar 1 lb.
Heavy-use size for treating infected stasis ulcers . . . burns . . . extensive skin areas or prolonged treatment.

- ■ broad-spectrum microbicidal action—kills both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), fungi, viruses, protozoa and yeasts
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HELPS TO REMOVE:

- Necrotic Tissue and Associated Odor

HELPS PREPARE WOUND FOR:

- Granulation/Healing
- Granulation/Grafting

CLEANSE WOUND
Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials.

THOROUGHLY MOISTEN
Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g., sodium chloride or water solutions).

APPLY ENZYME
Apply a layer of TRAVASE Ointment. Assure intimate contact with necrotic tissue and complete wound coverage.

APPLY MOIST DRESSING
Apply loose moist dressings (most important with dry leathery eschar).

CHANGE DRESSINGS
When changing dressing, gently wipe away the dissolved material. Repeat the procedure, including application of TRAVASE Ointment, 3 to 4 times per day for best results.

Travase® Ointment
brand of Sutilains

Travase® Ointment
brand of **Sutilains**

Description
TRAVASE® (brand of sutilains) Ointment is a sterile preparation of proteolytic enzymes, elaborated by Bacillus subtilis, in a hydrophobic ointment base consisting of 95% white petrolatum and 5% polyethylene. One gram of ointment contains approximately 82,000 casein units of proteolytic activity.

Indications
For wound debridement (1,2)—TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:
Second and third degree burns,
Decubitus ulcers,
Incisional, traumatic, and pyogenic wounds,
Ulcers secondary to peripheral vascular disease.

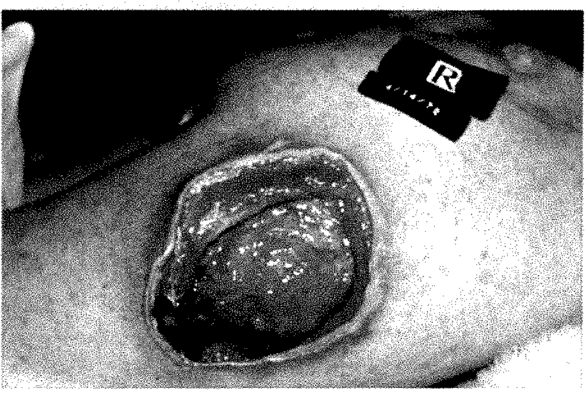
FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Please see next page for prescribing information.

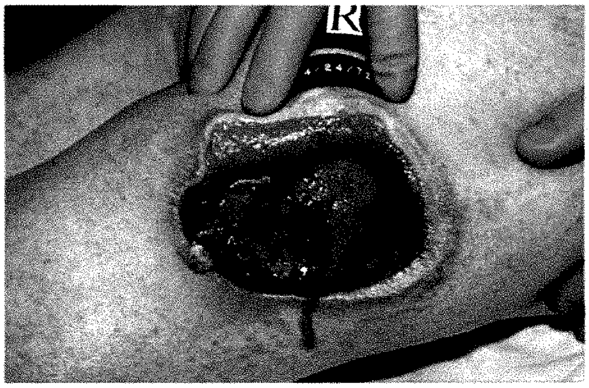
Travase® Ointment brand of Sutilains

ulcers

TERRY V. CARLE, M.D., CLINICAL INSTRUCTOR, DEPT. OF PHYS. MED. & REHAB.,
CRAIG REHABILITATION HOSPITAL, UNIVERSITY OF COLORADO



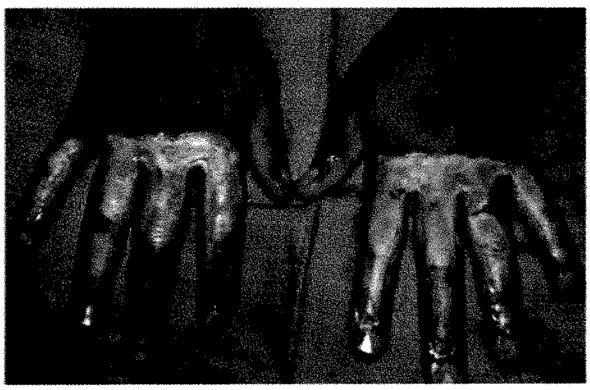
Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



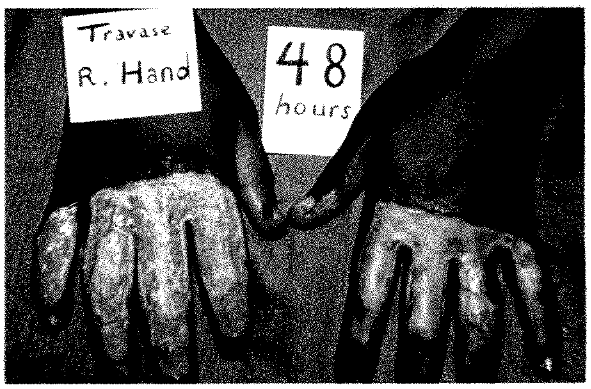
After nine days of TRAVASE therapy, debridement is nearly complete and granulation evident.

burns

DALE B. DUBIN, M.D., DIPLOMATE,
AMERICAN BOARD OF PLASTIC SURGERY, TAMPA, FLORIDA



Before treatment . . .



48 hours following treatment with TRAVASE Ointment on right hand; left hand is control.

Travase® Ointment

(brand of Sutilains)

Indications: For wound debridement, TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

- Second and third degree burns,
- Decubitus ulcers,
- Incisional, traumatic, and pyogenic wounds,
- Ulcers secondary to peripheral vascular disease.

Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

- Wounds communicating with major body cavities,
- Wounds containing exposed major nerves or nervous tissue,
- Fungating neoplastic ulcers,
- Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE upon the developing fetus.

Warning: Do not permit TRAVASE Ointment to come into contact with the eyes. If contact is made, immediately rinse with copious amounts of water, preferably sterile.

Precautions: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents (see package insert). Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

DOSAGE AND ADMINISTRATION: STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT:

1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g. sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

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Hypoxemia After Upper Abdominal Surgery:

Comparison of Venous Admixture and Ventilation/Perfusion Inequality Components, Using a Digital Computer

JANET NAIDL SILER, M.D., HENRY ROSENBERG, M.D.,
THOMAS D. MULL, M.D., JOEL A. KAPLAN, M.D., PENN COMPUTER
TRAINEES, HILLEL BARDIN, A.B. BRYAN E. MARSHALL, M.D.

From the Department of Anesthesiology and Institute for Environmental Medicine, University of Pennsylvania Medical Center, Philadelphia, Pa.

ARTERIAL HYPOXEMIA following upper abdominal surgery has been noted for varying periods of time, ranging from a few hours to several days.[10,16] Factors causing this disturbance in pulmonary oxygen exchange appear to be other than those produced by general anesthesia. In patients without abdominal incisions, hypoxia is reversed within the first 3 post-operative hours.[12] However, it is not clear whether in the presence of an abdominal incision, a decreased arterial oxygen tension is due solely to atelectasis (shunting)[4] or to a mixture of shunting and altered ventilation/perfusion ratios.[7] In the present study, we have estimated the relative effects of venous admixture and ventilation/perfusion inequality on hypoxemia for several days following upper abdominal surgery.

Material and Methods

Twenty patients 21 to 68 years of age without known respiratory or cardiovascular disease from routine history, physical examination, chest X-ray and EKG consented to be studied pre-operatively and on the first, third and sixth post-operative days. Arterial blood gases were measured at rest while breathing room air and after breathing 100% oxygen for 10 minutes via a nose clip, rubber mouth piece and non-rebreathing Ruben valve. Expired oxygen per cent was measured with a Beckman Oxygen Analyzer to detect the presence of any leaks within the system, as well as the adequacy of denitrogenation. Minute ventilation and respiratory frequency were recorded while the patients breathed 100% oxygen. The blood gas determinations were performed using an Instrumentation Laboratories analyzer for pH, pCO_2 and pO_2. Base Excess was calculated from the Severinghaus slide rule. All values were corrected to BTPS.

Calculation of the alveolar-arterial oxygen tension difference ($P_{AO_2} - P_{aO_2}$) was made on 100% oxygen and assumed due to venous admixture. The sample syringes contained heparin in their dead space and 50 torr was added to the measured oxygen tension to correct for this.[5] A total $P_{AO_2} - P_{aO_2}$ on room air was also obtained. We calculated the per cent venous admixture that would cause the $P_{AO_2} - P_{aO_2}$ while breathing 100% oxygen and assumed this same per cent to be present while breathing room air and recalculated the $P_{AO_2} - P_{aO_2}$ that would result. This amount was subtracted from the total $P_{AO_2} - P_{aO_2}$ on room air, and the remainder was due to ventilation/perfusion inequality. A digital computer program was employed for these calculations and is found in Appendix A and B. For this purpose we assumed an arterio-venous respiratory gas exchange ratio of 0.8.

Submitted for publication January 13, 1973.

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Reprint requests: Janet Siler, M.D., Department of Anesthesia, Nazareth Hospital, 2601 Holme Avenue, Philadelphia, Pennsylvania 19152.

Statistical analysis of the data was done by using the paired "t" test. The "p" values were found using the two-tailed significant levels.

Results

The general information concerning the patients, surgical procedure and anesthetic technique appear in Table 1. Data for these 20 patients is presented as th solid line in Fig. 1. and Tables 2 and 3. The total $P_{A_{O_2}}$ - $P_{a_{O_2}}$ is significantly increased (p = <.01) on the firs third and sixth post-operative days. Venous admixtu is significantly increased (p = <.01) on the third an sixth post-operative days while on the first post-operativ day a "p" value of >.05 was found. On all 3 post-operativ

TABLE 1. *Patients, Surgical Procedure and Anesthetic Technique*

Age	Sex	Surgical Procedure	Type of Incision	Time (Hour)	Anesthetic Technique	Post-operative Analgesia
70	M	Gastroenterostomy Repair incisional hernia	Right upper paramedian	1½	Nitrous oxide Curare	Morphine sulphate
45	M	Lysis of adhesions Sigmoid colectomy Cecostomy Colo-colostomy	—	4½	Nitrous oxide Curare	Morphine sulphate
68	F	Cholecystectomy	Right Subcostal	1¾	Cyclopropane	Demerol
32	M	Exploratory laparotomy Subtotal gastrectomy	Upper midline	7	Cyclopropane Curare	Morphine sulphate
38	F	Cholecystectomy	Right Subcostal	1½	Cyclopropane Curare	Morphine sulphate
42	M	Subtotal gastrectomy Gastrojejunostomy Billroth II	Upper midline	5½	Penthrane	Morphine sulphate
56	M	Cholecystectomy Common bile duct exploration Operative Cholangiogram	Right subcostal	3	Nitrous oxide Curare Fentanyl	Morphine sulphate
35	F	Cholecystectomy Choledochostomy Common bile duct exploration Appendectomy	Right subcostal	3	Cyclopropane Succinylcholine	Demeral
46	M	Exploratory laparotomy Biopsy of pancreatic tumor	Left subcostal	1¾	Nitrous oxide Curare	Morphine sulphate
31	M	Gastrectomy Vagotomy Gastro-jejunostomy	—	5	Halothane Curare	—
57	M	Left colectomy Cecostomy Appendectomy	Midline below linea semilunaris and left paramedian above	5½	Cyclopropane Curare	Morphine sulphate Pentazocine
33	F	Cholecystectomy Operative cholangiogram	Right subcostal	3½	Nitrous oxide Curare	Demerol
56	M	Subtotal gastrectomy Gastro-jejunostomy Billroth II Vagotomy Gastrostomy	—	10	Ethrane Curare	Morphine sulphate
43	M	Hemi-gastrectomy Vagotomy Liver biopsy	Upper Midline	4¾	Nitrous oxide Curare	Demerol
24	M	Partial gastrectomy Vagotomy Gastrostomy Welch duodenostomy	—	6	Nitrous oxide Curare	Morphine sulphate Demerol
57	M	Common bile duct exploration	Right subcostal	2	Nitrous oxide Curare	Morphine sulphate
28	M	Subtotal gastrectomy Vagotomy Gastro-jejunostomy	Upper midline	4	Cyclopropane Curare	Morphine sulphate
60	M	Exploratory laparotomy Appendectomy	Upper and Lower midline	2¾	Cyclopropane Curare	Morphine sulphate
73	M	Anterior resection of sigmoid colon	Upper and Lower midline	3½	Halothane Curare	Morphine sulphate
32	M	Repair of hiatal hernia	—	2¾	Penthrane	Morphine sulphate

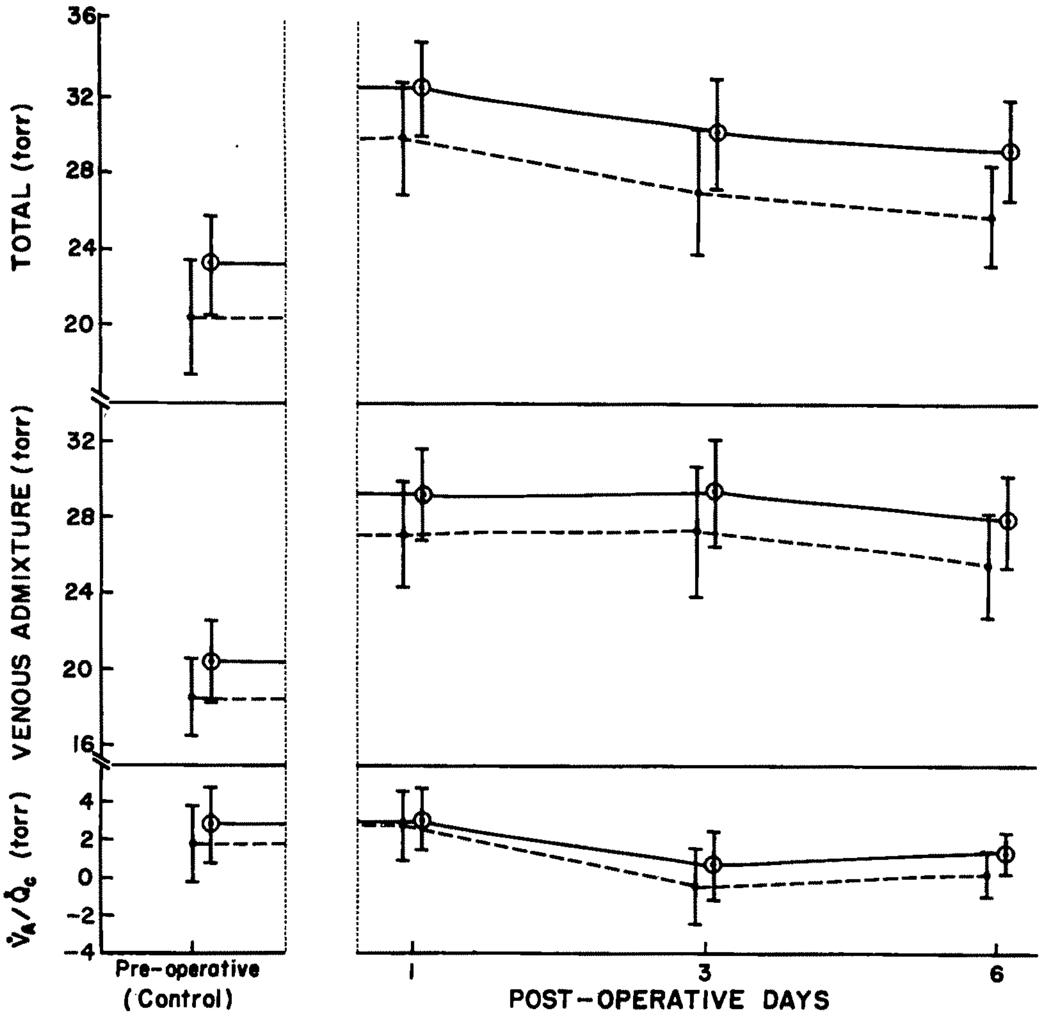

FIG. 1. In all 3 boxes, the the $P_{A_{O_2}} - P_{a_{O_2}}$ in 20 patients is represented by the solid line, while the broken line represents the $P_{A_{O_2}} - P_{a_{O_2}}$ in 15 "normal" patients. The upper box gives the total $P_{A_{O_2}} - P_{a_{O_2}}$ while the middle shows the venous admixture component and the lower box gives the amount of the $P_{A_{O_2}} - P_{a_{O_2}}$ due to ventilation/perfusion inequality.

days, ventilation/perfusion inequality was not significantly changed.

Of the 20 patients studied, 5 were found to have pulmonary abnormalities post-operatively both clinically and radiographically. The remaining 15 "normal" patients are graphically presented in Fig. 1. as the dotted line. Numerical values for components of the $P_{A_{O_2}} - P_{a_{O_2}}$ are found in Table 3. Statistical analysis revealed the following information. The total $P_{A_{O_2}} - P_{a_{O_2}}$ was significantly increased the first post-operative day (p = <.01). On the third and sixth post-operative days, the increased $P_{A_{O_2}} - P_{a_{O_2}}$ was significant at p = <.05 level. Venous admixture on all 3 post-operative days was significantly increased (p = <.01). Ventilation/perfusion inequality was not significantly changed on all three post-operative days (p = >.05).

TABLE 2. *Arterial Blood Gas Values in 20 Patients*
(*mean* ± *S.E.*)

		$P_{a_{O_2}}$ torr	$P_{a_{CO_2}}$ torr	pH units	B.E. mEq/L.
Pre-op	AIR	83 ± 2	36 ± 1	7.467 ± .007	2.7 ± .6
	O_2	579 ± 14	34 ± 1	7.499 ± .012	3.6 ± .7
Post-op	1 AIR	72* ± 3	38 ± 1	7.449 ± .010	2.4 ± .6
	O_2	476 ± 25	37 ± 1	7.448* ± .010	1.8 ± .4
	3 AIR	77 ± 3	35 ± 1	7.490* ± .009	3.9 ± .5
	O_2	512* ± 23	33 ± 1	7.511 ± .010	4.0 ± .5
	6 AIR	80 ± 2	35 ± 1	7.473 ± .006	1.9 ± .6
	O_2	537* ± 15	32 ± 1	7.498 ± .008	2.5 ± .4

* = Indicates difference from Pre-operative value significant $p < .01$ from "t" test.

TABLE 3. *Components of* $P_{A_{O_2}} - P_{a_{O_2}}$ *Difference*
(*mean* ± *S.E.*)

		Patients	Total torr	$\dot{Q}s/\dot{Q}t$ torr	$\dot{V}_A/\dot{Q}_C$ torr
Pre-op		20	23 ± 3	20 ± 2	2 ± 2
		15	20 ± 3	18 ± 2	2 ± 2
Post-op	1	20	32* ± 2	29 ± 2	3 ± 2
		15	30* ± 3	27* ± 3	3 ± 2
	3	20	30* ± 3	29* ± 3	1 ± 2
		15	27 ± 3	27* ± 3	0 ± 2
	6	20	29* ± 3	28* ± 2	1 ± 1
		15	26 ± 3	26* ± 3	0 ± 1

* = Indicates difference from pre-operative value significant $p < .01$ from "t" test.

For the individual patients with known pulmonary abnormalities, those with atelactasis had a marked increase in their venous admixture component post-operatively. The patient with known pulmonary emboli had an unusual increase in his ventilation/perfusion inequality with a lessening of his venous admixture component.

The lowest $P_{a_{O_2}}$ values occurred on the first post-operative day, with a return toward normal on the third and sixth day after operation. Significant acidosis was found while breathing 100% oxygen the first post-operative day. On the third post-operative day, significant alkalosis occurred while breathing room air.

Discussion

Post-operative hypoxemia in other than thoracotomy patients was first noted by Nunn and Payne.[15] Subsequently, it was found that arterial oxygen tension returned to pre-operative values 3 hours following surgical procedures not involving thoracic, abdominal or oral incisions and remained such 24 hours later.[10] Following abdominal surgical procedures, hypoxemia has persisted for several days.[10,11,16] This has been attributed to ventilation/perfusion inequalities and/or pulmonary shunt because of micro-atelectasis, changes in surfactant, changes in ventilatory patterns with the accompanying incisional pain, analgesics, a combination of these or other yet unknown factors.[13,19]

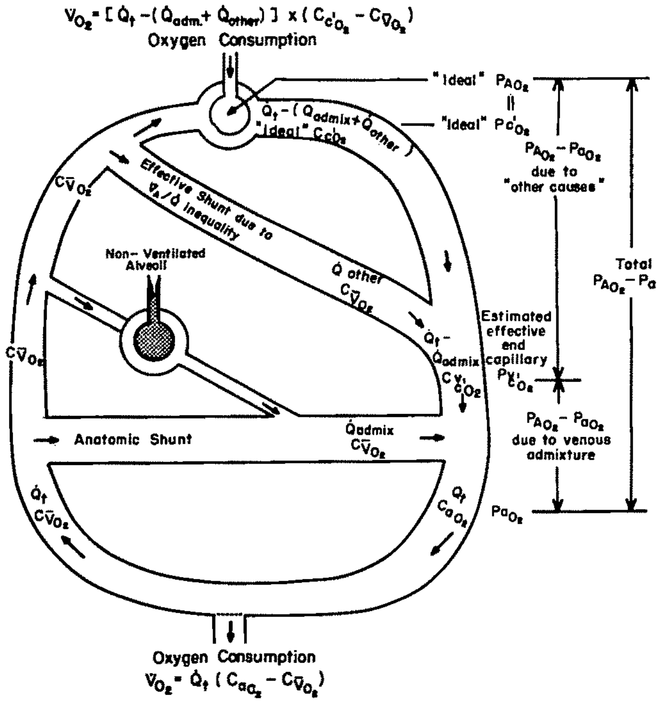
$V_{O_2} = [\dot{Q}_t - (\dot{Q}_{adm.} + \dot{Q}_{other})] \times (C_{c'_{O_2}} - C_{\bar{v}_{O_2}})$
Oxygen Consumption
"Ideal" $P_{A_{O_2}}$
‖
"Ideal" $P_{c'_{O_2}}$
$\dot{Q}_t - (Q_{admix} + \dot{Q}_{other})$
"Ideal" $C_{c'_{O_2}}$
$P_{A_{O_2}} - P_{a_{O_2}}$ due to "other causes"
$C\bar{v}_{O_2}$
Effective Shunt due to $\dot{V}_A/\dot{Q}$ inequality
Non-Ventilated Alveoli
$\dot{Q}$ other $C\bar{v}_{O_2}$
Total $P_{A_{O_2}} - P_{a_{O_2}}$
Estimated effective end capillary $P_{c'_{O_2}}$
$\dot{Q}_t - \dot{Q}_{admix}$ $C_{c'_{O_2}}$
$C\bar{v}_{O_2}$
Anatomic Shunt
$\dot{Q}_{admix}$ $C\bar{v}_{O_2}$
$P_{A_{O_2}} - P_{a_{O_2}}$ due to venous admixture
$\dot{Q}_t$ $C\bar{v}_{O_2}$
Q_t $C_{a_{O_2}}$
$P_{a_{O_2}}$
Oxygen Consumption
$\dot{V}_{O_2} = \dot{Q}_t (C_{a_{O_2}} - C\bar{v}_{O_2})$

FIG. 2. Schematic diagram represents a double shunt model of $P_{A_{O_2}} - P_{a_{O_2}}$. See Appendix A for discussion.

The results of this study indicate that venous admixture is the predominant cause of hypoxemia in these post-operative patients. The increasing venous admixture component of the alveolar/arterial oxygen tension was apparent in all patients without clinical or radiologic evidence of pulmonary abnormalities. This increase may be due to undetected areas of microatelectasis, closure of airways or increased flow through pulmonary artero-venous shunts.

Those patients undergoing a normal post-operative course demonstrated a fairly consistent pattern of change. The $P_{a_{O_2}}$ reached a minimum on the first post-operative day, was decreased on the third day and was returning toward normal by the sixth day. This time course and the predominance of the venous admixture component suggest that mechanical factors related to posture and the surgical incisions were of etiological importance. Closure of small airways with subsequent atelectasis is a likely sequence in those conditions which favor a reduction of functional residual capacity,[1] absence of frequent deep inspirations and relative immobility in the supine position. It may be possible to reverse these changes with the judicious application of a modest (2–5 cm H_2O) continuous end expiratory pressure. However, in the "normal" course of $P_{a_{O_2}}$ change this would not be necessary or desirable. It remains for future studies to demonstrate how this general response pattern is modified by other variables such as those listed in Table 1. The present sample was not designed to yield such detailed information.

This particular method of distinguishing between venous admixture and ventilation/perfusion inequality appeared to be helpful for the early diagnosis of pulmonary abnormalities. In the patient subsequently found to have had multiple pulmonary emboli at post-mortem, a marked increase in his ventilation/perfusion inequality over that of his venous admixture component was observed on the first post-operative day which preceded other clinical signs by approximately 24 hours. An increase of ventilation/perfusion inequality is a usual phenomenon with experimental pulmonary embolism. It has been attributed to both continued ventilation of non-perfused alveoli and disturbance of the reflex adjustment of blood flow to ventilation in the remaining alveoli. Venous admixture was significantly increased in patients showing radiologic evidence of atelectasis, but again the blood gas changes preceded clinical signs.

By using 2 arterial blood samples and the digital computer program, a practical and relatively simple means is available to not only identify patients at risk from arterial hypoxemia, but to identify or predict those patients departing from the normal pattern of recovery from major upper abdominal procedures. Also, a partial diagnosis of the cause of this departure can be assessed. The assessment may be more precisely determined if mixed venous blood is obtained or its oxygen content calculated from measurements of oxygen consumption and cardiac output. However such refinement is not routinely available while the relatively simple measurements described here do appear to have clinical importance in monitoring the post-operative course.

Summary

Alveolar-arterial oxygen gradients were studied in 20 patients following upper abdominal surgery with the assistance of a digital computer program for calculations. The oxygen gradient was separated into venous admixture and ventilation/perfusion inequality components. In those 15 patients without clinical or radiologic evidence of post-operative pulmonary abnormalities, the venous admixture component was significantly increased above the ventilation/perfusion inequality on the first and third post-operative days with a return towards normal by the sixth day. Patients with known atelectasis had an extra increase in their venous admixture component, while the patient with pulmonary emboli had a marked increase in ventilation/perfusion inequality and lessening of his venous admixture component. Changes in $P_{A_{O_2}} - P_{a_{O_2}}$ preceded other clinical evidence of pulmonary abnormality and appeared to have predictive value.

Appendix A

The computations may be divided into two parts:

I. Calculation of mean end capillary, arterial, and mixed venous oxygen contents for 100% O_2 and lower O_2 (e.g. room air) inspired gas mixes[18]; and

II. Calculation of effective shunts and alveolar minus arterial oxygen pressures, for the venous admixture and other (e.g. ventilation/perfusion inequality) components.

I. Calculation of oxygen contents(C'_{cO_2}. C_{aO_2}, $C_{\bar{v}O_2}$)

A. "Ideal" pulmonary end capillary oxygen tension (P'_{cO_2}) is assumed equal to "ideal" alveolar oxygen tension (P_{AO_2}).

B. Mean alveolar carbon dioxide tension (P_{ACO_2}) is assumed equal to arterial carbon dioxide tension (P_{aCO_2}), which is measured.

C. Water vapor pressure (P_{H_2O}) is estimated as a function of deep body temperature (T) by the quadratic relation:

$P_{H_2O} = .0625T^2 - 2.0625T + 37.81$[7] where P_{H_2O} is in torr, and T is in °C. (20)

Deep body temperature is measured in °C or °F; if fahrenheit, the program converts it to centigrade.

D. When breathing 100% O_2,

$P_{AO_2} = P_B - (P_{ACO_2} + P_{AH_2O})$ where P_B is the measured barometric pressure, and all pressures are in torr.

E. When breathing lower O_2, the program requires either an assumed respiratory exchange ratio (R) or the fractions of mixed expired oxygen ($F_{\bar{E}O_2}$) and carbon dioxide ($F_{\bar{E}CO_2}$). In either case, the fractions of inspired oxygen (F_{IO_2}) and carbon dioxide (F_{ICO_2}) are needed. All fractions are assumed dry and are converted to pressures (BTPS) by the relation:

$$P_x = F_x(P_B - P_{H_2O}) \text{ for any gas x.}$$

1. When R is given:

$$P_{AO_2} = ((P_{IO_2})R + (P_{ACO_2})(F_{IO_2})(- - R) + P_{ICO_2} - P_{ACO_2})/((F_{ICO_2})(1 - R) + R) \qquad (17)$$

2. When $F_{\bar{E}O_2}$ and $F_{\bar{E}CO_2}$ are measured:

$$P_{AO_2} = P_{IO_2} - P_{ACO_2}(P_{IO_2} - P_{EO_2}/P_{ECO_2}) \qquad (14)$$

F. The above steps yield P'_{cO_2} for both 100% O_2 and lower O_2.

G. The arterial oxygen tension (P_{aO_2}) is measured for both 100% O_2 and lower O_2.

H. The mixed venous oxygen pressures ($P_{\bar{v}O_2}$) may be measured, or else a fixed arterial to venous content difference ($C_{aO_2} - C_{\bar{v}O_2}$) may be entered.

I. The oxygen pressures are converted to % saturation using Kelman's formula (8, 9) based on Severinghaus' oxyhemoglobin dissociation curve. In addition to deep body temperature (T), arterial pH and Base Excess (B.E.) are entered, as well as mixed venous pH and B.E. if $P_{\bar{v}O_2}$ has been measured. End capillary calculations use the arterial values of pH and B.E.

Kelman's method first converts the actual P_{O_2} (at actual pH, B.E. and T) to a virtual P_{O_2} which, at standard pH, B.E. and T, yields the identical percent saturation. Virtual P_{O_2}(v) is given by:

$$v = (P_{O_2})(10^{0.48\,(pH - 7.4) - .0013\,B.E. - .024\,(T-37)})$$

where P_{O_2} is the actual oxygen pressure. The oxyhemoglobin percent saturation (S_{O_2}) is then given by

$$S_{O_2} = 100[(a_1v + a_2v^2 + a_3v^3 + v^4)]/[(a_4 + a_5v + a_6v^2 + a_7v^3 + v^4)]$$

where a_1 through a_7 are Kelman's coefficients as follows:

$a_1 = -8.5322289 \times 10^3$
$a_2 = 2.1214010 \times 10^3$
$a_3 = -6.7073989 \times 10^1$
$a_4 = 9.3596087 \times 10^5$
$a_5 = -3.1346258 \times 10^4$
$a_6 = 2.3961674 \times 10^3$,
$a_7 = -6.7104406 \times 10^1$

J. Calculation of the content of dissolved O_2 requires the Bunsen solubility coefficient of oxygen in blood (α). This value is approximated for deep body temperature in the range 32°C ≤ T ≤ 40°C by

$$\alpha = .0330 - .0003T + .000042e^{.153Hb} \qquad (3)$$

where

α is measured in ml O_2 STPD/ml whole blood/760 torr,
e is the base of the natural logarithms,
Hb is the hemoglobin concentration in gm/100 ml.

K. The oxygen content (C_{O_2}) is the sum of dissolved and bound oxygen.

$$C_{O_2} = (\alpha)(100/760)(P_{O_2}) + (1.39)(Hb)(S_{O_2}/100)$$

where C_{O_2} is in vol% (i.e. ml O_2/100 ml whole blood).

L. If P_{vO_2} was not measured, then an assumed value for ($C_{aO_2} - C_{\bar{v}O_2}$) is entered into the program. The content of mixed venous oxygen is then given by

$$C_{\bar{v}O_2} = C_{aO_2} - (C_{aO_2} - C_{\bar{v}O_2})$$

M. The above steps are followed to calculate six oxygen contents; namely "ideal" $C_{c'O_2}$, C_{aO_2} and $C_{\bar{v}O_2}$ for both 100% O_2 breathing and lower O_2.

II. *Calculation of Shunts and Resolution of Venous Admixture and Other Components*

A. Using the six oxygen contents previously calculated, it will be possible to resolve the total shunt on lower O_2 into components due to venous admixture and other (e.g. ventilation/perfusion inequality) causes.

B. Using the 100% O_2 breathing values, the total effective shunt as percent of cardiac output ($\dot{Q}_s/\dot{Q}_t$) is given by

$$\dot{Q}_s/\dot{Q}_t = 100[(C_{c'O_2} - C_{aO_2})]/[(C_{c'O_2} - C_{\bar{v}O_2})] \qquad (5)$$

This shunt is assumed due entirely to venous admixture, as other causes of alveolar-arterial P_{O_2} difference ($P_{AO_2} - P_{aO_2}$), e.g. ventilation/perfusion inequality (V_A/Q) or pulmonary diffusion impairment, disappear under 100% O_2. (Note that blood flow past non-ventilated alveoli is included in the venous admixture component.)

C. It is assumed that the shunt due to venous admixture, expressed as percent of cardiac output, remains constant on 100% O_2 or lower O_2. Therefore, the venous admixture portion of the effective shunt, when breathing lower O_2 equals the total shunt when breathing 100% O_2, which was calculated in the previous step. These relations are shown in Table 1a. Renaming the shunts yields Table 1b.

D. Using the values obtained from lower O_2 breathing, the total shunt on lower O_2 is calculated by the formula used in step 2 above. The effective shunt due to causes other than venous admixture is then obtained by subtracting the venous admixture component from the total.

E. Fig. 2. illustrates the model underlying the calculation of the two A-a components. If there were no venous admixture at all (i.e. neither anatomic shunt nor non-ventilated alveoli), there could still be an A–a difference due to other causes. We define a content $C_{\check{c}'O_2}$ which we call "estimated effective end capillary (ventilated)" oxygen content, such that "ideal" $C_{c'O_2} - C_{\check{c}'O_2}$ is the A–a content difference due to "other" causes alone. While this A–a difference is not the result of a real shunt, it is possible to postulate a venous shunt which, were it mixed with "ideal" end capillary blood, would yield the identical content $C_{\check{c}'O_2}$. This shunt would have a flow of $\dot{Q}_{other}$, and would have the same *effect* as the actual "other" causes of A–a difference.

The model assumes that his blood with lowered oxygen content is now mixed with more venous blood, i.e. the venous admixture, with a flow of $\dot{Q}_{admix}$, such that the final mixture has the content of arterial blood (C_{aO_2}). (This simplifying assumption may not be entirely correct, since some of the venous admixture possibly flows into the pulmonary capillaries).

The flow of oxygen into the arterial junction (in the model) must equal the flow of oxygen in the arteries. Since oxygen flow is $\dot{V}_{O_2} =$ $Q \times C_{O_2}$, it follows that

$$V'_{cO_2} + V_{admix\ O_2} = V_{aO_2}$$
$$(Q_t - Q_{admix}) \times C'_{cO_2} + Q_{admix} \times C_{vO_2} = Q_t \times C_{aO_2}$$
$$C'_{cO_2} = (Q_t \times C_{aO_2} - Q_{admix} \times C_{vO_2})/(Q_t - Q_{admix})$$
$$C'_{cO_2} = (C_{aO_2} - (Q_{admix}/Q_t) \times C_{vO_2})/(1 - (Q_{admix}/Q_t))$$
$$\dot{C}'_{cO_2} = (C_{aO_2} - (\%\text{Shunt on } 100\%\ O_2/100) \times C_{vO_2})/(1 - (\%\text{Shunt on } 100\%\ O_2/100))$$

TABLE 1. *Relationships of Effective Shunts Due to Venous Admixture and Other Causes*

1a

Effective Shunt Due To:	When Breathing 100% O_2	Lower O_2
Total (All Causes)	x	y
Venous Admixture Only	x	x
Other Causes (e.g. $\dot{V}/\dot{Q}$) Only	—	y – x

1b

Effective Shunt Due To	When Breathing 100% O_2	Lower O_2
Total (All Causes)	$\dot{Q}_{admix}/\dot{Q}_t$	$\dot{Q}_{admix} + \dot{Q}_{other}/\dot{Q}_t$
Venous Admixture Only	$\dot{Q}_{admix}/\dot{Q}_t$	$\dot{Q}_{admix}/\dot{Q}_t$
Other Causes (e.g. $\dot{V}/\dot{Q}$) Only	—	$\dot{Q}_{other}/\dot{Q}_t$

It is worth noting that this analysis differs from that in general use (2) and therefore gives somewhat different results.

F. Having found $C_{\check{c}'O_2}$ (i.e. the C_{aO_2} due to other causes) it is necessary to find the corresponding $P_{\check{c}'O_2}$. The program finds $P_{'\check{c}O_2}$ by employing a binary search and using the Kelman formulae (with arterial pH and B.E.) to check the oxygen contents corresponding to possible prospects for the correct P_{O_2}, until an extrêmely close approximation to $P_{\check{c}'O_2}$ is found.

G. The alveolar-arterial P_{O_2} difference due to venous admixture is simply $P_{c'O_2} - P_{aO_2}$, while that due to other causes is $P_{AO_2} - P_{\check{c}'O_2}$.

H. The preceding steps have resolved the total $P_{AO_2} - P_{aO_2}$ difference into components due to venous admixture and other (e.g. V_A/Q inequality) causes.

Appendix B

The computer program was written in the BASIC language and implemented on a Digital Equipment Corporation PDP-12 computer. Computations required approximately one second per experiment, with a period of some 2½ minutes per experiment required to print out the results on the teletype. The program can run, without modification, on most time-sharing systems. Copies of the program, together with instructions for its use, are available from: Librarian, Institute for Environmental Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104.

The computer program used was written by the Penn Computer Trainees, a group of black students from West Philadelphia High School, who are studying programming at the University of Pennsylvania's Institute for Environmental Medicine (C. J. Lambertsen, M.D. Director), as part of the Medical Center's HEP-UP Program to interest black students in bio-medical careers. The students in the group are Joyce Beecham, Olivia Billups, Constance Bush, Fatima Hill, Augustus Jones, Sandra Jordan, Ruth McNatte, Virginia Morrison, Juan Polk and Sylvia Wilson, and their instructor is Hillel Bardin. The students' work was supported in part by grants from the Josiah Macy Foundation and the Dolfinger-McMahon Foundation.

References

1. Alexander, J. I., Horton, P. W., Millar, W. T., Parikh, R. K., Spence, A. A.: The Effect of Upper Abdominal Surgery on the Relationship of Airway Closing Point to End Tidal Position. Clin. Sci., 43:137, 1972.
2. Ayres, S. M., Christiello, A., Grahovsky, E.: Components of Alveolar-arterial O_2 Difference in Normal Man. J. Appl. Physiol., 19(1):43, 1964.
3. Christoforides, C., Hedley-Whyte, J.: Effect of Temperature and Hemoglobin Concentration of Solubility of O_2 in Blood. J. Appl. Physiol., 27(5):592, 1969.
4. Diament, M. L., Palmer, K. N. V.: Venous/Arterial Pulmonary Shunting as the Principle Cause of Post-operative Hypoxaemia. Lancet, 1:15, 1967.
5. Farhi, L. E., Rahn, H.: A Theoretical Analysis of the Alveolar-arterial O_2 Difference with Special Reference to the Distribution Effect. J. Appl. Physiol., 7:699, 1955.
6. Fletcher, G., Barber, J. L.: Effect of Sampling Technique on the Determination of P_{aO_2} During Oxygen Breathing. J. Appl. Physiol., 21:463, 1966.
7. Hamilton, W. K., McDonald, J. S., Fisher, H. W., Bethards, R.: Post-operative Respiratory Complications. Anesthesiology, 25:607, 1964.

8. Kelman, G. R.: Calculation of Certain Indices of Cardio-Pulmonary Function Using a Digital Computer. Resp. Physiol., **1**:335, 1966.
9. Kelman, G. R.: Digital Computer Subroutine for the Conversion of Oxygen Tension into Saturation. J. Appl. Physiol., **12**(4):1375, 1966.
10. Knudsen, J.: Duration of Hypoxemia After Uncomplicated Upper Abdominal and Thoraco-Abdominal Operations. Anesthesia, **25**:372, 1970.
11. Latimer, R. G., Dickman, M., Day, W. C., Gunn, M. L.: Ventilatory Patterns and Pulmonary Complications After Upper Abdominal Surgery Determined by Pre-operative and Post-operative Computerized Spirometry and Blood Gas Analysis. Am. J. Surg., **122**:622, 1971.
12. Marshall, B. E., Millar, R. A. Some Factors Influencing Post-operative Hypoxaemia. Anesthesia, **20**:408, 1965.
13. Marshall, B. E., Wyche, M. Q.: Hypoxemia During and After Anesthesia. Anesthesiology, 37:178, 1972.
14. Nunn, J. F.: Indirect Determination of the Ideal Alveolar Oxygen Tension During and After N_2O Anesthesia. Br. J. Anaesth., **35**:8, 1963.
15. Nunn, J. F., Payne, J. P.: Hypoxaemia After General Anesthesia. Lancet, **2**:631, 1962.
16. Palmer, K. N. V., Gardiner, A. J. S.: Effect of Partial Gastrectomy on Pulmonary Physiology. Br. Med. J., **1**:347, 1964.
17. Rahn, H., Fenn, W. O.: A Graphical Analysis of the Respiratory Gas Exchange. Washington, D. C., Am. Physiol. Soc. 40, 1962.
18. Riley, R. L., Cournand, A.: "Ideal" Alveolar Air and the Analysis of Ventilation/Perfusion Relationships in the Lungs. J. Appl. Physiol., **1**:825, 1949.
19. Sellery, G. R.: A Review of the Causes of Post-operative Hypoxia. Can. Anaes. Soc. J., **15**:142, 1968.
20. Weast, R. C. (ed.): Handbook of Chemistry and Physics. Cleveland, Chemical Rubber Company, 1970.

The Role of Groin Dissection in the Management of Melanoma of the Lower Extremity

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WIDE LOCAL EXCISION AND SKIN GRAFTING have become accepted surgical practices in the management of melanoma of the lower extremity.[20] Controversy, however, still exists as to the role of the groin dissection.[15,18] That procedure, when easily performed in continuity with excision of the primary lesion, has been advocated by many.[3,5] When the location of the primary tumor precludes an in-continuity dissection, the efficacy of the procedure has been questioned.[15] Likewise, the anatomical extent and timing of the regional node dissection have generated considerable controversy. Because up to 42% of melanomas are located in the lower extremity,[4] we felt a review of our cases was indicated in an attempt to answer these questions. The series we report is unique in several respects. First, because of a diversity of opinion among a large staff of surgeons, both superficial or inguinal dissections (ID) and deep or inguino-iliac dissections (I-ID) were performed and are available for comparison. Secondly, all surgical specimens were cleared of fat and scrutinized for individual nodes, each of which was microscopically examined at 3 levels.[14] This process ensures a higher yield of occult metastases.

Material and Methods

All charts with the diagnosis of melanoma of the lower extremity were reviewed at the Presbyterian Hospital in New York City; excluded were cases with the pathological diagnosis of either superficial melanoma or Hutchinson's Freckle, cases with evidence of distant disease at the initial visit and those cases in which, for a variety of reasons, a regional node dissection was not performed. Each chart was analyzed for age and sex of the patient, location and size of the primary tumor, clinical and pathological status of the groin, details and complications of the procedure and long-term follow-up. No attempt was made to grade the tumor according to microscopic depth of invasion.[2] Cases were classified as either dead or alive at 5 years. Other authors[9,12,19] have demonstrated that this interval is an adequate, yet not definitive, period of follow-up.

Results

Incidence

During the period of the review 98 groin dissections were performed and 87 of these patients were followed for a minimum of 5 years. Of these 87 patients, 63 underwent inguinal dissection (ID) and 24 inguino-iliac dissection (I-ID). The average number of nodes recovered by the clearing technique was 14 in the former group (ID) and 23 in the latter (I-ID).

Survival

The overall 5-year cure rate for the inguinal group (ID) was 60% and 54% for the inguino-iliac (I-ID) (Table 1). When both groups were analyzed in terms of histopathological findings (Table 2), there was a direct correlation between survival and absence of nodal involvement. As also noted, there were 6 patients in the inguinal group (ID) and 5 in the inguino-iliac group (I-ID) with histologically positive nodes who were alive at 5 years. Of these 11 patients, 3 eventually died of their disease. Of the remaining 8 felt to be cured of their disease, 7 had microscopic involvement of only one in-

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TABLE 1. *Five Year Survival*

Five Years	Inguinal Dissections (ID)	Inguino-iliac Dissections (I-ID)
Alive	38 (60%)	13 (54%)
Dead	25 (40%)	11 (46%)
Total	63 (100%)	24 (100%)

guinal node while another patient had only 2 positive inguinal nodes.

Survival was also directly related to the preoperative clinical appraisal of the groin (Table 3). Among the prophylactic dissections (e.g. clinically negative groins) 72% and 69% survived 5 years but among the therapeutic dissections (e.g. clinically positive groins) only 15% and 36% survived 5 years. In addition, the 2 patients in the ID group who survived 5 years following a presumed therapeutic dissection, had negative nodes on microscopic examination and were free of disease 7 and 13 years respectively. In the I-ID group, of the 4 patients surviving 5 years after a therapeutic dissection, one patient who was free of disease at seven years had a single large (4 cm.) node involved by tumor, while the remaining 22 nodes were free of any metastases. The remaining 3 patients died of widespread melanoma in the sixth, seventh, and thirteenth postoperative years. Therefore, in this group of 6 patients who underwent therapeutic dissections and were alive at 5 years, there was only one survivor after excluding those patients with histologically negative nodes (e.g. clinically false positive groin evaluation) and those patients who died of their disease after the 5-year point. In this light, the difference in survival between the prophylactic and therapeutic dissection is even more distinct.

There was also an attempt to evaluate the accuracy of the preoperative clinical groin evaluation in predicting the histological status of the regional lymph nodes (Table 4). The false negative rate was 16% in the ID group and 21% in the I-ID group, indicating that despite multiple examinations in a teaching hospital setting, there was a significant inability to detect occult nodal metastases in the preoperative period.

TABLE 2. *Histopathological Findings*

Inguinal Dissections (ID)

Five Years	Inguinal Nodes Negative	Inguinal Nodes Positive
Alive	33	6
Dead	11	13
Total	44	19

Inguino-iliac Dissections (I-ID)

Five Years	Ing. Neg. Iliac Neg.	Ing. Pos. Iliac Neg.	Ing. Pos. Iliac Pos.	Ing. Neg. Iliac Pos.
Alive	8	5		
Dead	3	4	3	1
Total	11	9	3	1

TABLE 3. *Clinical Status of the Groin*

Inguinal Dissections (ID)

Five Years	Clinically Negative Groin	Clinically Positive Groin
Alive	36 (72%)	2 (15%)
Dead	14 (28%)	11 (85%)
Total	50 (100%)	13 (100%)

Inguino-iliac Dissections (I-ID)

Five Years	Clinically Negative Groin	Clinically Positive Groin
Alive	9 (69%)	4 (36%)
Dead	4 (31%)	7 (64%)
Total	13 (100%)	11 (100%)

Satellitosis

A surgeon who performs a groin dissection in discontinuity theoretically runs the risk of entrapping malignant cells in those lymphatices situated between the primary lesion and the regional nodes. When this complication occurs, there is little hope of effecting a cure. In the inguinal dissection (ID) group 13 patients (21%) developed satellitosis. Ten of the 24 patients (42%) in the I-ID group developed this complication either during or after the 5-year period of follow-up.

Both groups were further subdivided to determine what percentage of patients, whose regional nodes were free of tumor, went on to develop in-transit metastases, Of the 44 patients in the ID group with pathologically negative groins 7 (16%) developed satellitosis as did 5 of 11 patients (46%) in the I-ID group. When analyzed from both aspects those patients undergoing an inguino-iliac (I-ID) dissection had a significantly higher rate of in-transit metastases.

Role of the Ten Day Delay

It has been postulated that a planned time lapse between the primary excision and the regional node dissection would be beneficial by allowing lymphatic clearance of any tumor emboli. Table 5 presents the survival and satellitosis rates of both groups when subdivided on

TABLE 4. *Correlation Between the Clinical and Histological Evaluation of the Regional Nodes*

	True	False Negative	False Positive
Inguinal Dissections (ID)	51 (81%)	10 (16%)	2 (3%)
Inguino-iliac Dissections (I-ID)	18 (75%)	5 (21%)	1 (4%)

TABLE 5. *Role of the Ten Day Delay*

Inguinal Dissections (ID)	Satellitosis	5 Yr. Survival
Before 10 Days (48 Pts.)	7 (15%)	30 (63%)
After 10 Days (15 Pts.)	5 (33%)	8 (53%)
Inguino-iliac Dissections (I-ID)	Satellitosis	5 Yr. Survival
Before 10 Days (15 Pts.)	6 (40%)	11 (73%)
After 10 Days (9 Pts.)	4 (44%)	2 (22%)

the basis of a 10-day delay between both surgical procedures.

In both groups, the delay failed either to enhance survival or decrease the percentage of patients developing satellitosis. In fact, the reverse was true in the group of patients whose regional node dissection was delayed by at least 10 days. However, it should be noted that the delay group was preselected as these patients tended to have had inadequate surgical, and often detrimental, non-surgical therapy prior to referral to this institution. The answer to this question awaits a prospective study.

Complications

There was no operative or perioperative death associated with either type of groin dissection. Wound problems were the most common complication. Seventeen of the 63 patients (27%) of the ID group had wound complications (e.g. seromas, infections, flap necrosis) and 4 of the 17 required secondary skin grafting. In the I-ID group, 7 patients (29%) developed these complications and 2 of the 7 required secondary skin grafting. With improved surgical technique and the use of suction catheters, these problems have decreased in recent years.

Lymphedema was graded significant only if the complaint persisted 3 months past surgery or if the complaint necessitated readmission to the hospital. Four patients (6%) of the ID group had chronic problems with lymphedema, compared to 11 patients (46%) of the I-ID group. Moreover, 2 of the 4 in the ID group had significant tumor recurrences in the lower extremity at the time that they developed lymphedema.

Discussion

Southwick[16] earlier defined the problem: "The question is how to treat a malignant disease, which may be regional or systemic in distribution when first seen without undertreatment of those patients in whom the disease is curable." Studies[7–9] have shown that survival is directly related to regional lymph node involvement and this is confirmed in the present study. Other authors[8,10,12] have reported a large error in the preoperative evaluation of the groin and Stehlin,[19] in a recent review, states that 5–50% of patients believed to have clinically uninvolved nodes had microscopic metastases on histological examination. In the present study, respective figures were 21% for the I-ID group and 16% in the ID group. Consequently deferring the regional node dissection could entail permitting a high percentage of patients to harbor their nodal metastases.

Das Gupta,[4] in reviewing the literature, quoted a 5-year cure rate of 0–24% for those patients undergoing therapeutic (e.g., clinically positive groin) node dissection. In the present study only 6 patients of this group were alive at 5 years. However, 3 of the 6 patients proved to have histologically negative nodes on pathologic study. In addition, 3 of these patients died of their disease after the 5-year interval. Overall, there was only one long-term survivor of a therapeutic dissection, if one excludes those patients whose preoperative groin evaluations were false-positive and those patients who died of melanoma after the 5-year mark.

In an attempt to avoid a regional node dissection in those patients who would be cured by wide local excision alone, some surgeons have advocated delaying the groin dissection until the regional nodes become suspicious on palpation. However, the Queensland Melanoma Project[10] reported that 14.6% of those patients who underwent prophylactic node dissections were dead at 5 years. The figure, however, rose to 35.7% for those patients who were observed prior to having a therapeutic dissection when they developed clinically suspicious nodes. Southwick[16] reported a 5-year survival of 80% in the prophylactic group versus 32.9% in a group initially observed and later subjected to a therapeutic dissection. Goldsmith[6] showed a similar fall-off between both subgroups. Moreover, 29 of the 71 patients in the observed group[16] went on to develop clinical evidence of regional node metastases. Similarly, one-third of the patients in the Queensland Melanoma Project[10] and 23% of the patients reported by McNeer[11] in the observed category eventually developed lymph node metastases.

In comparing the results of the inguinal dissections (ID) with the inguino-iliac dissections (I-ID), Fortner[5] reported a 38% 5-year survival in the former and a 43% figure for the latter. In our series, 60% of the patients undergoing a superficial dissection were alive at 5 years, compared to 54% in the inguino-iliac (I-ID) group.

In the large Memorial Hospital series,[5] there was only one patient who had pelvic nodal metastases without involvement of the inguino-femoral chain. There were 46 patients with positive nodes in both the inguinal and iliac groups. However, we quote directly from an accompanying qualifying statement: ". . . or information in the chart was insufficient to preclude deep node involvement." Only 4 (8.7%) of this group survived 5 years. In the Presbyterian Hospital series, no patient with iliac node involvement survived 5 years. In addition, only 4 of the 24 patients undergoing a deep (I-ID) dissection had iliac node involvement. It appeared, therefore, that involvement of the iliac chain was both a late and fatal development.

Approximately 20% of all groin dissections are complicated by the phenomenon of satellitosis;[12] Fortner[5] reported this complication in 18% of the Memorial Hospital group. In our series, if one includes all lower extremity recurrences, 42% of the inguino-iliac dissections and 19% of the inguinal dissections eventually (e.g. bebeyond the 5-year mark) developed this complication.

Petersen *et al.*[13] noted that staging the primary excision and regional node dissection by a delay of 14 days or more resulted in fewer patients developing metastases in the region of the primary tumor. Fortner,[5] however, failed to show any improvement in survival with a 1–3 month delay. In the present series, a delay of 10 days or more did not improve either the survival or satellitosis statistics. However, the answer to this question awaits a prospective study as the delayed group was heavily composed of patients who had received less than ideal therapy prior to referral to this hospital.

While in the present study local wound problems were equally present in both groups, chronic lymphedema, a serious problem in 46% of the patients in the I-ID group, occurred in only 7% of the superficial (ID) group. Byron[1] has reported a respective difference of 36% and 29% between both groups.

Conclusions and Summary

A high degree of inaccuracy in the clinical evaluation of lymph node status has been demonstrated in the present study. There is also a markedly lower survival rate for therapeutic dissections. Salvage is essentially restricted to those patients whose regional lymph nodes contain no metastases or have only microscopic involvement. In view of these findings, we continue to advocate prophylactic groin dissections. Because there were no survivors with iliac node involvement and because the iliac dissection adds considerable morbidity with chronic lymphedema, we feel the groin dissection should not be carried into the pelvis.

References

1. Byron, R. L., Lamb, E. J., Yonemoto, R. H. and Kase, S.: Node Dissection in the Treatment of Cancer. Surg. Gynecol. Obstet., **114**:401, 1962.
2. Clark, W. H., From, L., Bernardino, E. A. and Mihm, M. C.: The Histogenesis and Biologic Behavior of Primary Human Malignant Melanomas of the Skin. Cancer Res., **29**:705, 1969.
3. Conway, H., Hugo, N. E., and McKinney, P.: Excision of Glands in Continuity for Malignant Melanoma. Arch. Surg., **94**:129, 1967.
4. Das Gupta, T.: Current Concepts of Malignant Melanoma. Surgery Annual. 183, (1970).
5. Fortner, J. G., Booher, R. J., Pack, G. T.: Results of Groin Dissections for Malignant Melanoma in 220 Patients. Surg., **55**:485, 1964.
6. Goldsmith, H. S., Shah, J. P., and Kim, D. H.: Prognostic Significance of Lymph Node Dissection in the Treatment of Malignant Melanoma. Cancer, **26**:606, 1970.
7. Guiss, L. W., MacDonald, I.: The Role of Radical Regional Lymphadenectomy in Treatment of Melanoma. Am. J. Surg., **104**:135, 1962.
8. Gumport, S. and Meyer, W. M.: Treatment of 126 Cases of Malignant Melanoma. Ann. Surg., **150**:989, 1959.
9. Lane, N., Lattes, R., and Malm, J.: Clinicopathological Correlations in a Series of 117 Malignant Melanomas of the Skin of Adults, Cancer, **11**:1025, 1958.
10. McLeod, R., Davis, N. C., Herron, J. J., Caldwell, R. A., Little, J. H., and Quinn, R. L.: A Retrospective Survey of 498 Patients with Malignant Melanoma. Surg. Gynecol. Obstet., **126**:99, 1968.
11. McNeer, S. and Das Gupta, T.: Prognosis in Malignant Melanoma. Surgery, **56**:512, 1964.
12. Moore, G. E., and Gerner, R. E.: Malignant Melanoma. Surg. Gynecol. Obstet., **132**:427, 1971.
13. Petersen, N. C., Bodenham, D. C., and Lloyd, O. C.: Malignant Melanoma of the Skin: A Study of the Origin, Development, Etiology, Spread, Treatment, and Prognosis, Part II. Brit. J. Plast. Surg., **15**:97, 1962.
14. Pickren, J. W.: Significance of Occult Metastases. A Study of Breast Cancer. Cancer, **14**:1266, 1961.
15. Polk, H. C., Cohn, J. D., and Clarkson, J. G.: An Appraisal of Elective Regional Lymphadenectomy for Melanoma. Curr. Top. Surg. Res., **1**:121, 1969.
16. Southwick, H. W., Slaughter, D. P., Hinkamp, J. F., and Johnson, F. E.: The Role of Regional Node Dissection in the Treatment of Malignant Melanoma. Arch. Surg., **85**:63, 1962.
17. Spratt, J. S., Shieber, W., Dillard, B. M.: Anatomy and Surgical Technique of Groin Dissection. St. Louis, C. V. Mosby, 1965.
18. Staley, G. J.: A Consideration of Prophylactic Lymph Node Dissection. Surg. Clin. N. Am., **43**:49, 1963.
19. Stehlin, J. S.: Malignant Melanoma: An Appraisal. Surgery, **64**:1149, 1968.
20. Wilson, R.: Malignant Melanoma. A Follow-Up Study. West. J. Surg., **66**:29, 1958.

Effects of the Fiberoptic Laparoscope and Colonoscope on Morbidity and Cost

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ADVANCES IN FIBEROPTIC TECHNOLOGY provide the opportunity to substitute several endoscopic operations for conventional surgical procedures. Percutaneous tubal ligation through the fiberoptic laparoscope has been substituted successfully for transvaginal or transabdominal ligations.[2,4] The fiberoptic colonoscope can visualize, biopsy, and usually remove all pedunculated polyps from rectum to cecum,[5] thus avoiding the complications and extended hospital stay of transabdominal polyp surgery.[3]

This paper examines the medical and economic implications of introducing this new technology at a major university hospital.

Methods

The period of study chosen was from January, 1971 to May 31, 1972. The laparoscope and colonoscope were introduced in the late fall of 1971 and replaced laparotomies in all cases where tubal ligation or resection of pedunculated polyps was the primary reason for operating. The population consisted of all patients who underwent tubal ligation or colonic polypectomy, except those who had these operations performed secondary to other surgical procedures. The latter were excluded from the study to avoid misleading data on cost and morbidity.

The operating room log of the Peter Bent Brigham Hospital was searched to obtain the study populations. For each eligible patient, biographical, medical, and cost information was abstracted from hospital records. A follow-up was done for all patients in the study to determine whether the patient was still alive 30 days after the operation, how the patient was feeling, and when normal activities were resumed. All the patients with polypectomies were followed up, as were 98% of patients with tubal ligations. The 2 patients lost to follow-up were known to be alive and to have moved from Massachusetts.

The Eder fiberoptic laparoscope with Pilling light source was used for the laparoscopic tubal ligations. This instrument and its accessories cost approximately $1,700. Under direct visualization, the Fallopian tubes were grasped in their mid portion, and using cautery, a section of each Fallopian tube was removed.

For colonoscopic polypectomies, the Olympus fiberoptic colonoscope Model CFSB with light source Model 0110-0 was passed to remove pedunculated polyps from rectum to mid-transverse colon. It cost approximately $3,500.

Results

Tubal Ligations

Fifty-three women had transvaginal or transabdominal tubal ligations and 32 women had laparoscopic tubal ligations. The mean age of women undergoing each type of tubal ligation was similar (Table 1.), as was racial composition. Women undergoing transvaginal or transabdominal tubal ligation had an average of 4.1 living

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TABLE 1. *Sex, Age, Length of Stay, and Complications*

		Tubal Ligation		Colonic Polypectomy	
		Laparotomy	Laparoscope	Laparotomy	Colonoscope
Number of Patients		53	32	17	9
Sex	No. Male			10	3
	No. Female			7	6
Mean Age		31.4	31.5	65.8	62.3
Mean Length of Stay		5.7*	2.6*	13.8**	4.4**
% of Patients with Complications	Serious	23%†	3%†	35%‡	0%‡
	Mild	53%	22%	41%	22%

* $p < 0.001$ (evaluated with Student t table)[1]
** $p < 0.001$ (evaluated with Student t table)[1]
† Chi-squared (with continuity correction) = 4.46; $p < 0.05$
‡ Chi-squared (with continuity correction) = 2.38; $p > 0.05$

children, compared to 3.6 living children for women undergoing fiberoptic sterilization.

Complications were more frequent and serious following laparotomies (Table 1). These serious complications included one case of postoperative bleeding that necessitated a hysterectomy 3 days after hospital discharge, 2 pregnancies unrecognized during tubal ligation which resulted in therapeutic abortions at 17 weeks and at 5 months, one perforation each of the cervix, small bowel, and uterus. There were 2 additional cases of intraoperative blood loss of 500 ml or more. Four other patients had the following complications: acute peritonitis, atelectasis, pelvic abscess, and severe reactive depression. The most frequent mild complication was a fever of 100° to 102°.

The one serious complication among the 32 laparoscopic tubal ligations was a failure of tube transsection, which was suspected when the pathology laboratory failed to identify the right tubal lumen. The patient underwent a hysterosalpingogram which confirmed the failure of transsection. She was readmitted for a right laparoscopic tubal transsection. Pain from CO_2 insufflation and sore throat from general anesthesia were the most frequent mild complications.

On follow-up, it was determined that women undergoing laparotomy on the average returned to work or their usual activities at 29 days, compared to 14 days for women who had the endoscopic procedure. On the average, women resumed sexual relations 54 days after transvaginal or transabdominal tubal ligation, and at 23 days following laparoscopic tubal ligation.

Cost analysis (Table 2) showed that transvaginal or transabdominal tubal ligations were 1.4 times more expensive than laparoscopic tubal ligations. The daily room charges increased during the study period, thus minimizing the real differences in cost. Cost distribution for laparoscopic tubal ligations showed savings for all expenditure categories except surgeon's and anesthesiologist's fees.

Colonic Polypectomies

Seventeen patients had transabdominal colonic polypectomies and 9 patients had colonoscopic polypectomies. The mean age of patients undergoing each type of colonic polypectomy was similar (Table 1), as was racial composition.

Following transabdominal polypectomies, surgical complications were more frequent, serious and varied than following endoscopic removal (Table 1). The national mortality experience following this operation is 1%–2%.[4] One of the 17 patients who had a polypectomy via laparotomy died 3 weeks later of a myocardial infarct. This 63-year-old man had previously been in excellent health. In addition, there were the following serious complications: intraoperative splenic rupture, serious postoperative bleeding, peritoneal infection, and 2 cases of wound infection. The most frequent mild complication was a low-grade postoperative fever. In contrast, there were no serious complications following polypectomy

TABLE 2. *Average Charges*

	Tubal Ligation		Colonic Polypectomy	
	Laparotomy	Laparoscope	Laparotomy	Colonoscope
Surgeon's Fee	$ 286.	$ 250.	$ 300.	$ 244.
Anesthesiologist's Fee	218.	232.	167.	—
O.R. and R.R.	438.	311.	465.	158.
Room/Board	492.	241.	1,320.	404.
Lab	140.	87.	475.	161.
All Other	140.	94.	514.	108.
Total	$1,714.	$1,215.	$3,241.	$1,075.
	$p < 0.001$*		$p < 0.001$*	

* Evaluated with Student t table[1]

through the colonoscope during the study period.* Two patients had mild abdominal discomfort.

Follow-up showed that patients undergoing polypectomy via laparotomy returned to work or their usual activities on average at 32 days, compared to an average of 2 days for patients undergoing the endoscopic procedure.

Categorical cost analysis (Table 2) demonstrated that the polypectomy via laparotomy was 3 times more expensive than the colonoscopic polypectomy. An anesthesiologist was not needed for any of the 9 colonoscopic polypectomies. Moderate sedation using morphine, nembutal or atropine, sufficed, supplemented as needed by intravenous morphine. Patients who underwent the endoscopic procedure also did not need to go to the recovery room. The surgeon's fee remained essentially unchanged, while all other expense categories showed important reductions.

Discussion

The laparoscope for tubal ligations and the colonoscope for pedunculated colonic polypectomies appear to have real advantages as measured by operative risks and costs. Wheeless[4] reported 100 outpatient laparoscopic tubal ligations under local anesthesia, with no serious postoperative complications. The anesthesiologist's fee, much of the operating and recovery room fee, and the cost of room and board can be eliminated if laparoscopic tubal ligations are done under local anesthesia and on an outpatient basis. At the Brigham this could further reduce the average cost from $1,214 to an estimated $481. Under current plans, this hospital will perform routine laparoscopic tubal ligations on an outpatient basis in 1973.

The patients operated on via the scope also returned to normal activities or employment earlier than those who had laparotomies. This represents another important saving which has not been included in the cost calculations.

As more surgeons develop expertise with the colonoscope, an increasing number of patients should be able to have polyectomies as outpatients. Shinya reported in a private communication that of a total of 430 colonoscopic polypectomies that he has performed, 55 of these have been done without complications in the outpatient department. His outpatients were younger, with smaller, pedunculated polyps, and with no cardiac or respiratory disease.

The use of increasingly complex technology has extended the realm of surgery into new areas, such as organ transplantation. Many of these developments have been associated with greatly increased complexities and costs. Surgery via fiberoptic scopes is an interesting exception insofar as it permits simplification of operations at reduced risks and costs for the patient. Although this study suggests great advantages for ambulatory endoscopic procedures, it would be desirable that proof be obtained by random clinical trial of out-patient and inpatient care to assure comparability of patients and real differences in outcome and cost.

Summary

This study was done to determine whether new surgical technology could achieve important reductions in morbidity and cost. Surgical operations which have been greatly simplified by 2 advances in fiberoptics were considered: the laparoscope to replace transvaginal or transabdominal tubal ligations and the colonoscope to replace transabdominal pedunculated colonic polypectomies. With the laparoscope, serious operative complications were reduced from 23% to 3%, while cost was reduced by 30%. With the colonoscope, serious operative complications were eliminated, while average cost decreased by two-thirds. The performance of both procedures via fiberoptic scope appears to have important advantages for the patient in reduction of complications and cost.

Acknowledgments

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References

1. Aspin, A. A.: Tables for Use in Comparisons Whose Accuracy Involved Two Variances, Separately Estimated, with an Appendix by BL Welch. Biometrika, 36:290, 1949.
2. Cohen, M. R.: Laparoscopy, Culdoscopy, and Gynecography. Philadelphia, W. B. Saunders Co., 1970.
3. Welch, C. E.: Polypoid Lesions of the Gastrointestinal Tract. Philadelphia, W. B. Saunders Co., 1964.
4. Wheeless, C. R.: Outpatient Laparoscope Sterilization Under Local Anesthesia. Obstet. Gynecol., 39:767, 1972.
5. Wolff, W. I. and Shinya, H.: Colonfiberoscopy. JAMA, 217: 1509, 1971.

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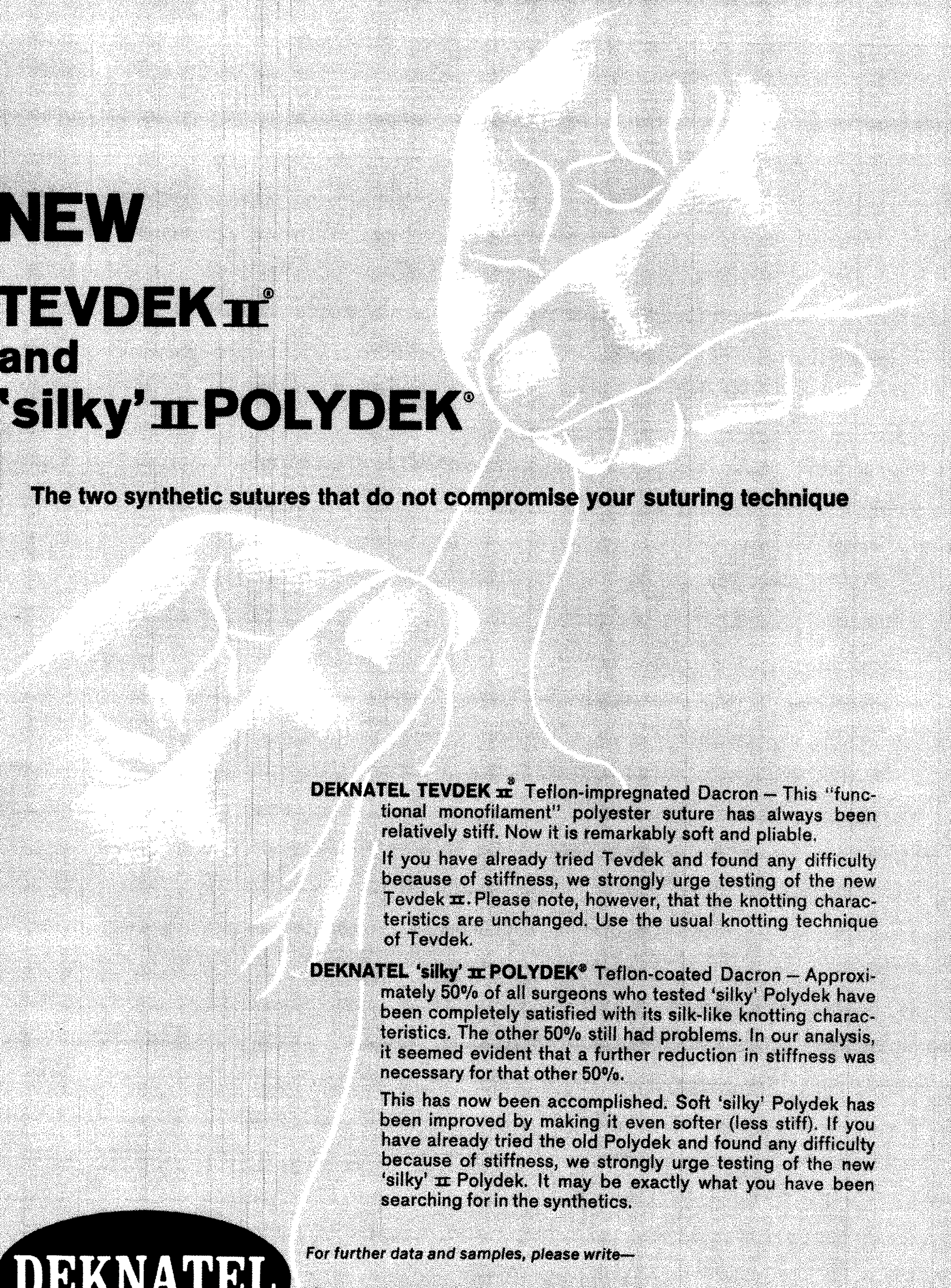
* Between October 1971 and September 1972, 122 diagnostic colonoscopies and 43 colonoscopic polypectomies were performed. A single major complication occurred in July (after the study ended)—the perforation of a sigmoid diverticulum. The patient underwent transabdominal polypectomy and bowel plication uneventfully.



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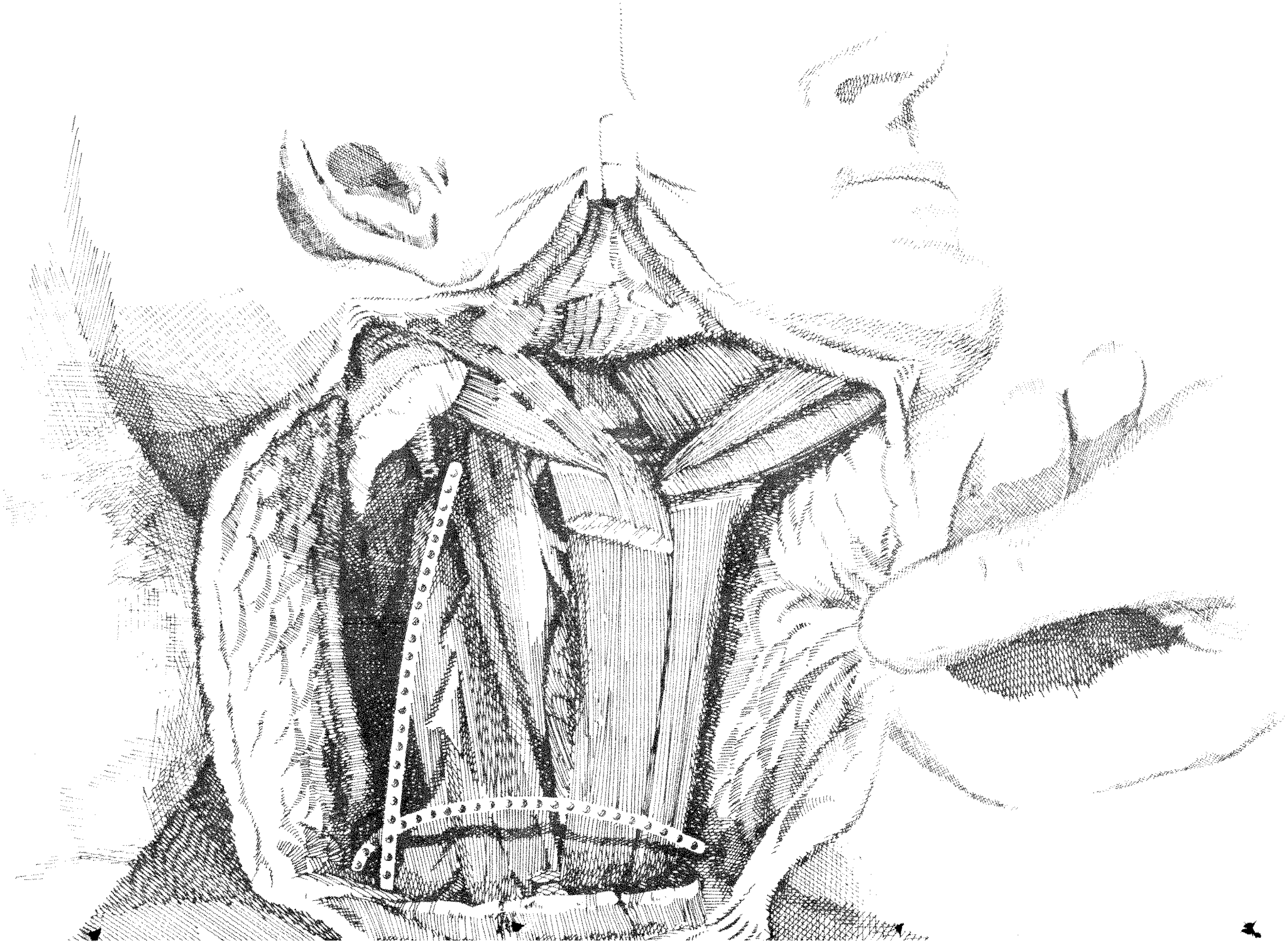

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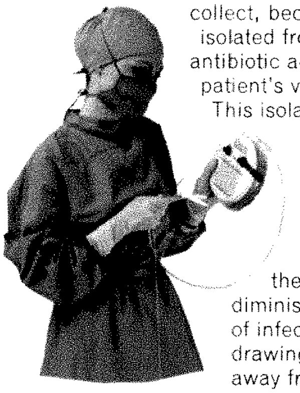

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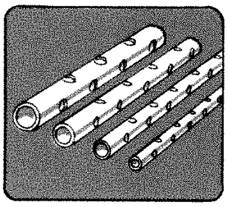

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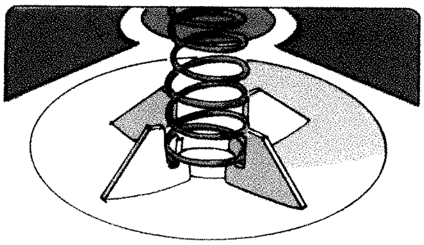

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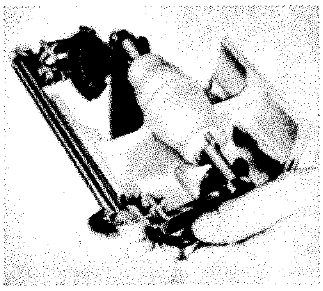

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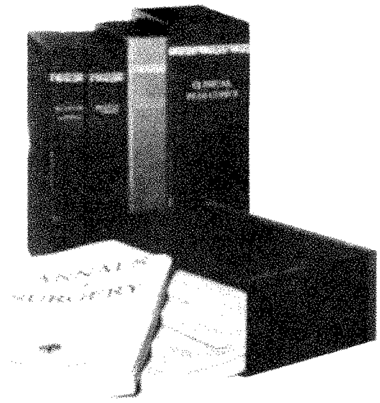

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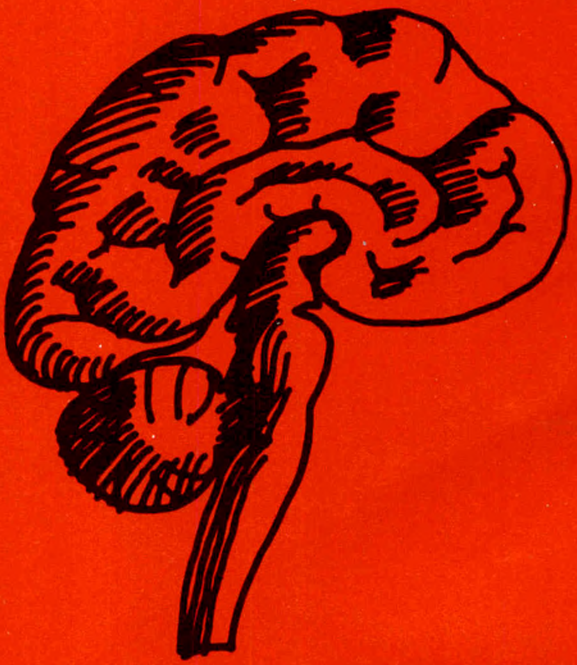

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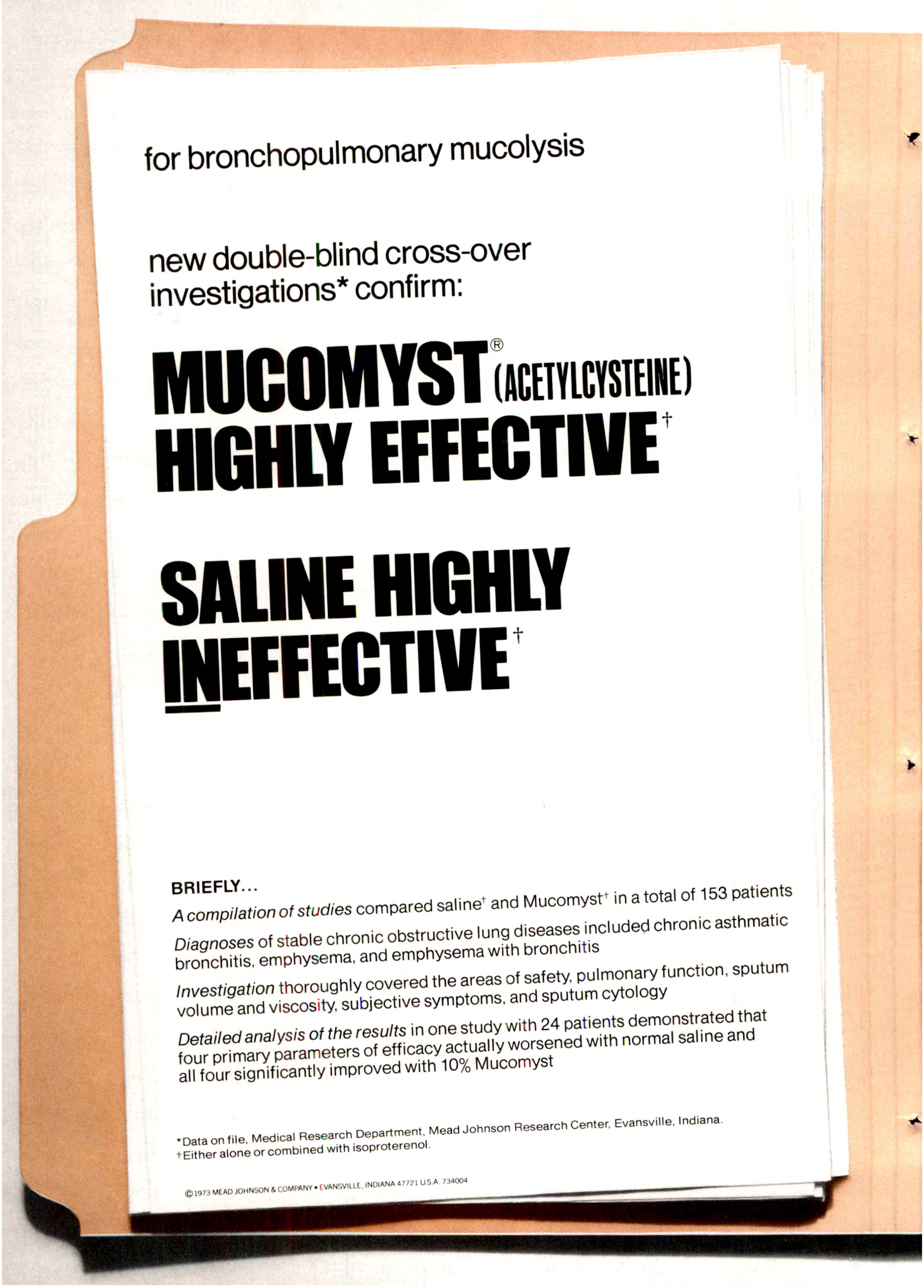

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Detailed analysis of the results in one study with 24 patients demonstrated that four primary parameters of efficacy actually worsened with normal saline and all four significantly improved with 10% Mucomyst

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*Data on file, Medical Research Department, Mead Johnson Research Center, Evansville, Indiana.

[†] Either alone or combined with isoproterenol.

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MUCOMYST VS. SALINE

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One double-blind cross-over study which included analysis of 52 variables compared the effects of one week of normal saline therapy with the effects of one week of 10% Mucomyst in each of 24 patients.

While large changes cannot be expected after one week's therapy in patients with stable chronic obstructive lung disease, of the variables that changed significantly with saline therapy, more worsened than improved. However, of the variables that changed significantly with Mucomyst, the great majority were *improvements* in the patients' status.

	Variables	
	Improved	Worsened
Mucomyst	13	2
Saline	4	5

CONCLUSIONS

- Mucomyst decreases sputum viscosity—saline *at best* effects no change
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- Mucomyst *reduces* the length of the expiratory phase—saline causes no change or increases it

Therapeutic compatibility of Mucomyst with isoproterenol and other bronchodilators has been demonstrated in double-blind controlled studies totaling 134 patients. No untoward effects requiring cessation of Mucomyst therapy were reported in these patients.

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Indications: Mucomyst has been demonstrated to be clinically effective as adjuvant therapy in a wide range of conditions in which thick, viscous mucus is a problem, including: postoperative atelectasis and pneumonia; chronic bronchopulmonary disease (emphysema, chronic bronchitis, asthmatic bronchitis, and bronchiectasis); acute bronchopulmonary disease (pneumonia, bronchitis, and tracheobronchitis); tracheostomy care; facilitation of bronchial studies; maintenance of an open airway during anesthesia; and to help control pulmonary complications of cystic fibrosis. **Contraindications:** Mucomyst is contraindicated in those patients who are sensitive to it. **Warnings:** *After proper administration of acetylcysteine, an increased volume of liquefied bronchial secretions may occur. When cough is inadequate, the open airway must be maintained by mechanical suction if necessary. When there is a large mechanical block due to foreign body or local accumulation, the airway should be cleared by endotracheal aspiration, with or without bronchoscopy. Asthmatics under treatment with Mucomyst should be watched carefully. If bronchospasm progresses, this medication should be immediately discontinued.* **Adverse Effects:** Adverse effects have included stomatitis, nausea and rhinorrhea. Sensitivity and sensitization to Mucomyst have been reported very rarely. A few susceptible patients, particularly asthmatics (see *Warnings*), may experience varying degrees of bronchospasm associated with the administration of nebulized acetylcysteine. Most patients with bronchospasm are quickly relieved by the use of a bronchodilator given by nebulization. **Administration:** Mucomyst may be administered by nebulization into a tent, Croupette, face mask, or mouthpiece, or by direct instillation. *Mucomyst should not be placed directly into the chamber of a heated (hot pot) nebulizer.* Complete details on dosage, administration, and compatibility are included in the package insert. Additional information may be obtained from Mead Johnson Laboratories. **Supplied:** *Mucomyst®-10 (acetylcysteine)* a sterile 10% solution in vials of 10 ml. and 30 ml.; *Mucomyst® (acetylcysteine)* a sterile 20% solution in vials of 10 ml. and 30 ml.

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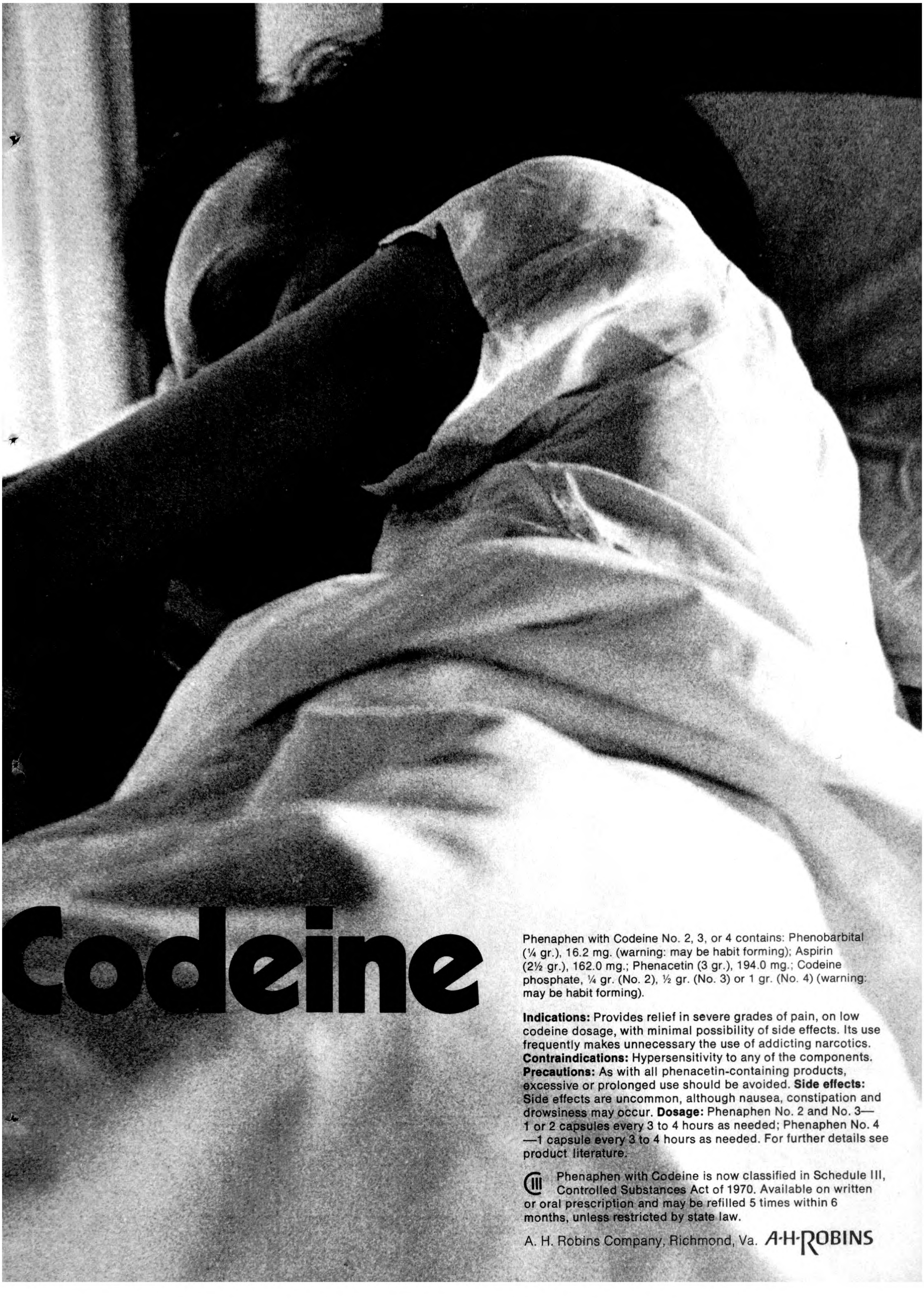

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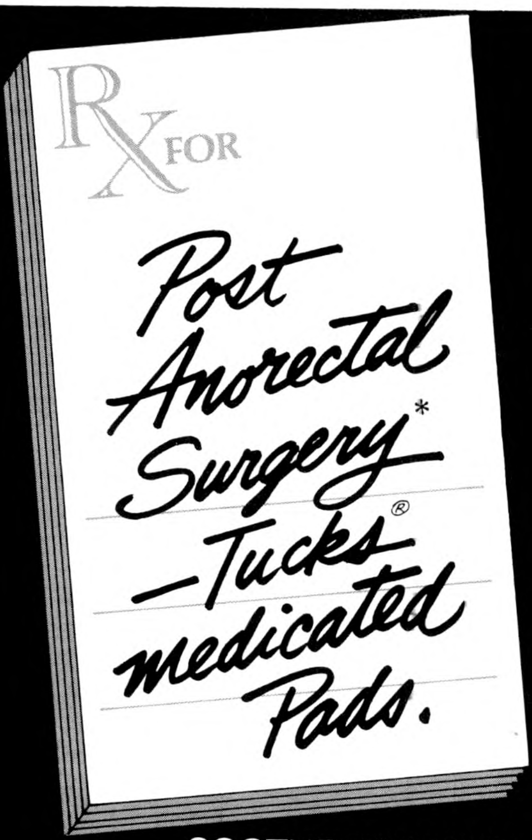

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*The Committee on Pre and Postoperative Care. American College of Surgeons: Manual of Preoperative and Postoperative Care. Second Edition. W. B. Saunders Co., Philadelphia, Pa., 1971, p. 423.

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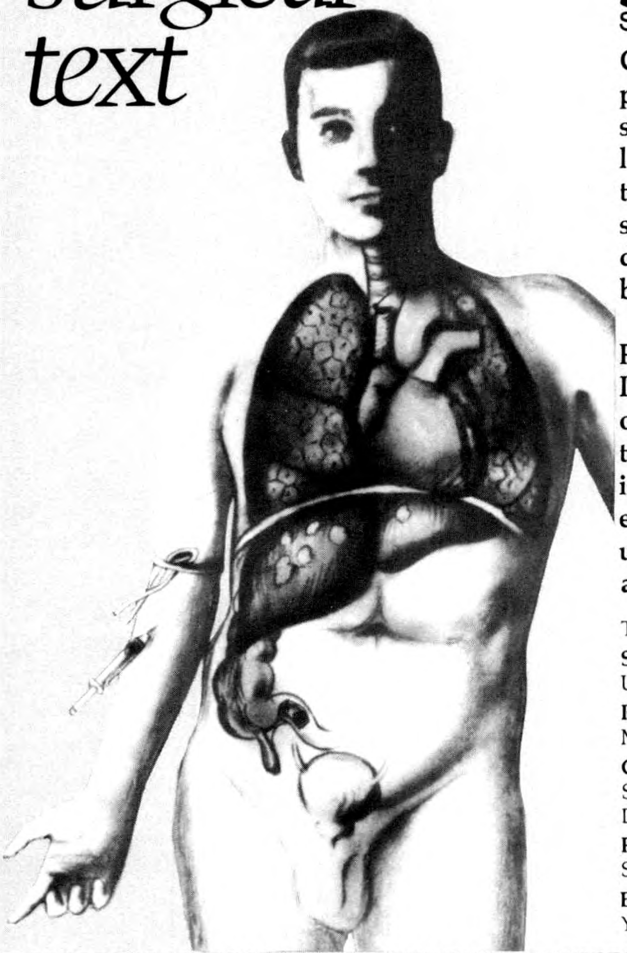

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The Effect of Anemia on Wound Healing

CHRISTOPHER HEUGHAN, B.A., M.B., B. CHIR., F.R.C.S.,*
GUNTA GRISLIS, B.A., THOMAS K. HUNT, M.D., F.A.C.S.

From the Department of Surgery, University of California School of Medicine, San Francisco, California and Trauma Center, San Francisco General Hospital, San Francisco, California

ANEMIA FREQUENTLY IS BLAMED for defective wound healing.[3,7,11,25] Most young surgeons today are taught that normal healing is jeopardized when the hematocrit falls below 35%. Each year countless blood transfusions are given to meet this arbitrary and questionable criterion despite the fact that it is supported neither by clinical nor experimental fact.

Three of 4 clinical surveys of patients with abdominal wound disruption have failed to implicate anemia as a major factor. Marsh,[19] Mann,[18] Alexander[2] and their co-workers found that anemia, uncomplicated by other deficiencies, did not contribute significantly to wound dehiscence. Guiney and his colleagues,[8] by contrast, found that 50% of their patients who disrupted their abdominal wounds were anemic as opposed to 20% of the control group who healed normally. However, their criterion of anemia, a hemoglobin of less than 12 gm/100 ml., was somewhat strict.

The results of experimental studies, without close analysis, appear conflicting. Besser and Ehrenhaft[5] found no decrease in the bursting strength of stomach wounds in dogs made anemic by bleeding and retransfusing pooled plasma. Trueblood and his co-workers[23] found no decrease in the bursting strength of colonic anastomoses in rats made anemic by iron deficiency or bleeding and retransfusion of plasma. Adamson[1] showed no difference in skin bursting strength with bleeding and retransfusion with plasma expander.

Results obtained by other investigators prove that nutritional deficiency incidental to the production of anemia accounts for some of the apparently conflicting results. Waterman, *et al.*[24] confirmed that anemia had no effect on either the contraction of open wounds or on the bursting strength of laparotomy incisions in young rats. They also showed that control as well as anemic rats fed powdered milk (a diet often used to produce iron-deficiency anemia) with and without added iron, showed slower contraction and reduced breaking strength when compared to animals fed normal chow. The chow-fed animals gained twice as much weight in the course of the experiment. Macon and Pories[17] also found that iron deficiency anemia had no effect on wound breaking strength and young rats fed on regular chow gained both body weight and wound tensile strength more rapidly than animals which were fed powdered milk with or without iron. Nutritional depletion, therefore, can explain the findings of Jacobson and Van Prohaska[15] whose chow-fed control mice showed a significantly higher breaking strength than the anemic group which was fed on an iron-free powdered milk diet. Bains, Crawford and Ketcham[4] reported decreased breaking strength in young rats (145–165 gm) made anemic by a combination of iron deficient diet and bleeding. However, iron deficiency in the young has a potent effect on growth rate and hence on repair.

Hugo and his colleagues[12] found a decrease in breaking strength in rabbits made anemic by hemolysis with intraperitoneal phenylhydrazine after 6 days, but there was no difference in strength at 9 or 12 days. The toxic potential of phenylhydrazine on wound metabolism is not known.

Abnormalties of blood volume or viscosity, both of which severely impair healing, may also co-exist with

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anemia. Sandblom[21] found decreased breaking strength in wounds of rabbits made anemic by bleeding. These animals were often dehydrated and hypovolemic. He later showed that dehydration can decrease wound strength. Sandberg and Zederfeldt[22] repeated these experiments but replaced blood volume with dextran and restored healing towards normal. When they denervated the wounded area, healing became entirely normal. Hunt, *et al.* demonstrated that hypovolemia severely decreases oxygen supply to the wound,[14] and wound hypoxia delays repair.[6,13]

Most of these studies relied upon measurement of breaking strength as the index of repair. Collagen accounts for the strength of wounds, and therefore any factor which affects the strength of early wounds must do so by interfering with collagen biosynthesis, or by accelerating collagen lysis. Collagen synthesis requires oxygen for several of its steps. Assembly of the amino acid chains on the ribosome is energy-dependent. Fibroblasts contain the enzymes for glycolysis, but most of their energy is ultimately derived from oxidative metabolism. Hydroxylation of some of the proline and lysine molecules, which is essential for structure and function of the collagen molecule, requires vitamin C, ferrous iron, α-ketoglutarate and molecular oxygen as essential cofactors for the hydroxylating enzyme.[16]

Under normal conditions the rate-limiting factor in collagen biosynthesis is the local availability of molecular oxygen. Niinikoski[20] and Hunt and Pai[13] have shown that the rate of gain in strength and collagen content in experimental wounds was greater when the animals breathed 45% to 60% oxygen and was less in an atmosphere of 12% oxygen as compared to control animals breathing air.

Obviously, oxygen is vital to healing, but the accumulated evidence heavily favors the conclusion that uncomplicated or moderated anemia does not affect wound healing. Nevertheless, surgeons continue to believe and teach that it does. Presumably the reason for this is the fundamental belief that red cell deficiencies *must inevitably* decrease oxygen delivery to the wound. Apparently this belief will persist until it is shown conclusively that anemnia does not decrease wound oxygen supply. The present study was undertaken, therefore, to demonstrate directly whether a mild, normovolemic anemia impairs oxygen delivery to experimental granulation tissue in the rabbit and secondarily, in a particularly discriminating model, whether this degree of anemia impairs accumulation of connective tissue.

Materials and Methods

Four stainless steel wire mesh cylinders were implanted subcutaneously in each of 25 New Zealand White male rabbits weighing 2 to 3 kg. After the cylinders had been implanted, approximately 12 ml. of blood were removed from every animal by cardiac puncture while anesthesia was continued. The red cells were separated by centrifugation and the serum was stored in a freezer.

Cardiac blood was withdrawn with a heparinized plastic syringe from a 20-gauge 1½ inch needle introduced into the xiphosternocostal angle about 30° from the horizontal and near the sagittal plane. This procedure can be done with the animal under mild sedation.

On day 11, wound fluid was aspirated from the wound cylinder and its oxygen tension and pH were measured.* The $pC0_2$ was determined by the Astrup method. This method of wounding, fluid sampling, and measurement has been described in detail by Hunt *et al.*[13]

The animals were divided into anemic and control groups, both of which were bled again by cardiac puncture 12, 13, 18 and 20 days later. Twelve to 20 ml. of blood were removed on the first 2 occasions and 24 to 30 ml. on the last. The serum from the anemic group was separated by centrifuging. Pooled plasma was made up to a volume equal to that of blood removed and was reinjected into an ear vein. The control animals were bled and retransfused with their own blood after a similar time lapse to that required for separating the plasma in the anemic group.

The pooled plasma was tested for agglutination of the recipient red cells of 6 animals at the begnning of the experiment. In no case was the reaction different from a control slide of red cells and serum from the same animal.

Blood for hematocrit and viscosity determinations was taken from an ear artery. Viscosities were measured with a cone-plate microviscometer† at 4 different shear rates. These determinations required only a total of 2 ml. of blood, and did not add significantly to the anemia.

The animals were killed with an overdose of pentobarbital on the twenty-second day and the wound cylinders were removed and opened. The connective tissue within was scraped off, defatted in three changes of 2/1 diethyl ether/acetone mixture and dried in an air oven to a constant weight.

Results

Several rabbits died from hemothorax after cardiac puncture. Several other animals in the group from which red cells were withdrawn failed to show a change in hematocrit, presumably because of concurrent dehydration. The data from these animals were discarded. Nine anemic animals and 8 controls formed the basis of the final data.

The packed cell volumes (P.C.V.) and wound fluid oxygen tensions are summarized in Fig. 1. The mean P.C.V. in the control group remained steady at 38%. The P.C.V. of the anemic animals in the last period of the experiment, when collagen is synthesized most rapidly in this model, was 30%. The differences in P.C.V. between the anemic and control groups were statistically significant on days 15, 18, and 22 (Fig. 1).

---

* Radiometer gas monitor, Copenhagen N.V., Denmark.

† Brookield Engineering Laboratories Inc. Stoughton, Mass. Model LVT.

Wound oxygen tensions were identical in both groups. The possibility that the oxygen tensions of the 2 groups could significantly differ on any day is less than 2%. Carbon dioxide tension and pH were also identical (Table 1).

Dry weights of new connective tissue are also shown in Table 2. The anemic group produced 12% more connective tissue by dry weight than the control. This difference is significant ($p < 0.025$). In previous work we have shown that dry weight of this tissue is an excellent measure of collagen content. The hydroxproline content of this tissue is constantly 44 μg/mg collagen. Several "spot samples" of tissue in this experiment showed this ratio in both groups.

The mean whole blood viscosity at a shear rate of 1.15 seconds^{-1} in controls was 6.4 ± 0.4 (S.E.) centapoise and remained stable throughout the experiment. As soon as the anemia was induced, viscosity fell 19% to 5.2 ± 0.3 centapoise. This was a significant difference, $p < 0.02$. The differences at the 3 higher shear rates were also statistically significant.

Discussion

The role of dead space gas tensions in reflecting the oxygen economy of an experimental wound has been described by Hunt and his associates.[18] Oxygen diffuses from the capillary loops and is extracted by the wound cells, thereby maintaining a large gradient across the wound edge. The oxygen tension of the wound fluid in the "dead space" represents the lowest average extracellular pO_2 in the wound.[13] The magnitude of this gradient is dependent upon the mean capillary pO_2 (and therefore upon the arterial oxygen tension) as well as upon the rate of oxygen extraction by the wound cell population for respiration, protein synthesis and proline hydroxylation.

The mean capillary pO_2 is maintained by transfer of oxygen from red cells to plasma. This process in turn depends on the oxygen content of the red cell, on the efficiency of the transfer of oxygen from red cell to plasma, and on the rate of flow of red cells through the wound capillaries.

In this study the red cell density of the general circulation was reduced in the anemic group. However, the decrease in whole blood viscosity and consequent increase in cardiac output tend to increase the rate of passage of red cells through the wound. Furthermore, the transfer of oxygen from the erythrocytes to the plasma is likely to become more efficient due to an increase in intracellular 2:3 diphosphoglycerate (2:3 D.P.G.) concentration. These are normal physiological responses to anemia and tend to restore normal oxygen delivery. These factors are apparently partly responsible for the increase in connective tissue synthesis in anemic animals.

If anemia were to diminish the oxygen supply to the extracellular fluid adjacent to the wound capillaries, one of 2 things would have to happen: 1) the quantity of oxygen extracted by the cells would remain constant, in which case cell function would be maintained and healing would proceed normally. Less oxygen would then remain to diffuse into the dead space and the pO_2 there would drop. 2) Alternatively the oxygen consump-

TABLE 1. *Anemia*

			Day		
		11	15	18	22
Hct. %	anemia	39 ± 1.7	39 ± 2 *	39 ± 1 *	38 ± 1 *
	control		32 ± 1	34 ± 1	30 ± 1
$p0_2$	anemia	8.3	9 ± 2	10 ± 2	10 ± 2
	control		10 ± 2	11 ± 2	9 ± 2
pH	anemia	7.09	7.09	7.09	7.12
	control		7.11	7.08	7.11
$pC0_2$	anemia	66.3	72	68	66
	control		67	68	67
Dryweight mg.	anemia				240 ± 10 mg*
	control				213 ± 10

* Statistically significant ($p < 0.025$).
All other differences are not significant.

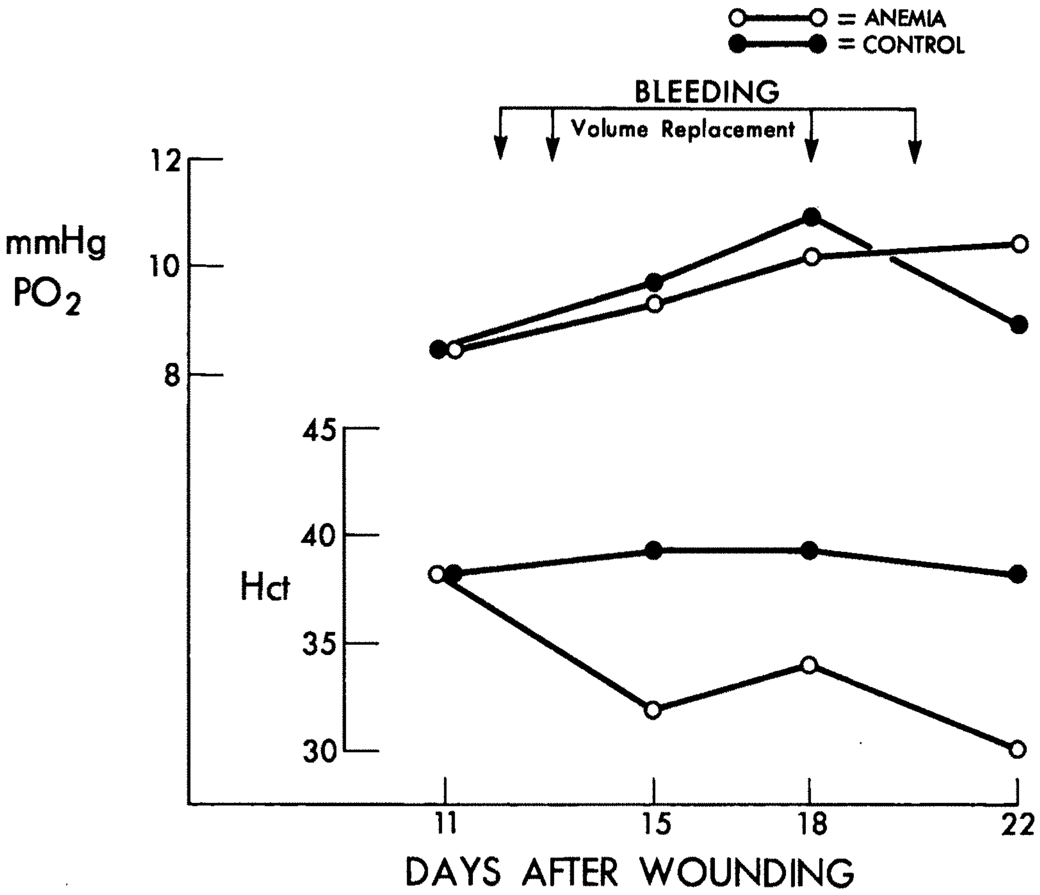

FIG. 1. The changes in packed cell volume and wound-fluid oxygen tension are shown. The oxygen tensions in the two groups are statistically not different, but the differences in packed cell volume are significant on days 15, 18, and 22.

tion of the wound cells would decrease with the supply, causing the oxygen gradient across the wound to become less steep. In this case the oxygen tension of the wound fluid might remain constant, but the weight of tissue synthesized in the chamber would inevitably diminish.[6] Experimentally, however, the pO_2 of the dead space remained constant, and the tissue synthesis was increased by the anemia. Therefore, neither of these possibilities occurred. Obviously, anemia did not diminish oxygen supply. Arterial pO_2, not oxygen content, is the quantity which overwhelmingly governs oxygen supply to the wound. This is not a revolutionary concept. It merely recognizes that vascular damage has occurred in the wound and that oxygen supply is, therefore, limited by the rate at which oxygen can diffuse across the avascular space of the wound. Pressure, not volume of gas, determines the rate of diffusion.

The experimental model used in this study has previously demonstrated the effects of an impaired oxygen supply under several experimental circumstances. Diminishing arterial pO_2 from normal to 45 mm Hg lowers dead space pO_2 from 10 to 7 mm Hg and significantly lowers connective tissue accumulation. Raising blood viscosity by Dextran 500 infusion also produces a significant fall in pO_2 and tissue synthesis.[10] Obviously this model is capable of detecting subtle changes in oxygen supply.

The present study demonstrates that mild, uncomplicated, normovolemic anemia, which commonly occurs in surgical patients undergoing an otherwise uneventful recovery does not require blood transfusion, with its attendant dangers, to achieve optimal healing. This probably does not apply to severe anemia in which other deficiencies may co-exist, or in which the compensatory mechanisms may be overwhelmed or impaired.

Common sense dictates that at some point, anemia inevitably will impede wound healing. This point has not been determined precisely and may be in the range of a P.C.V. of 15 according to Zederfeldt.[26] Recently, Adamsons[1] has shown that a hemoglobin of 5 to 6 gms. (P.C.V. approximately 20) fails to impede repair in animals.

Summary

The existing evidence linking "anemia" with healing is critically reviewed. Experimentally, no significant change occurred in the oxygen economy of experimental wounds in normal rabbits made anemic by bleeding and retransfusing plasma. Connective tissue synthesis was slightly greater at a P.C.V. of 30% than at a P.C.V. of 40%.

Healing is impaired by conditions which are often associated with anemia such as malnutrition, abnormalities of circulating blood volume, and increased blood viscosity following trauma. However, mild or moderate, uncomplicated, *normovolemic* anemia in otherwise healthy individuals does not impair delivery of oxygen to the wound and is of no consequence to wound healing. Anticipated stimulation of wound healing is *not* reason for transfusion to correct mild or moderate normovolemic anemia.

References

1. Adamsons, R. J.: The Effect of Profound Anemia On Wound Healing. J. Surg. Res. (In press).
2. Alexander, H. C. and Prudden, J. F.: The Causes of Abdominal Wound Disruption. Surg. Gynec. Obstet., **122**:1223, 1966.
3. Arey, L. B.: Wound Healing. Physiol. Rev., **16**:327, 1966.
4. Bains, J. W., Crawford, D. T. and Ketcham, A. S.: Effect of Chronic Anemia on Wound Tensile Strength. Correlation With Blood Volume, Total Proteins, Total Red Blood Cell Volumes. Ann. Surg., **164**:243, 1966.
5. Besser, E. L. and Ehrenhaft, J. L.: The Relationship of Acute Anemia to Wound Healing. Surgery, **14**:239, 1943.
6. Ehrlich, H. P., Grislis, G. and Hunt, T. K.: Metabolic and Circulatory Contributions to Oxygen Gradients in Wounds. Surgery, **72**:578, 1972.
7. Glenn, F. and Moore, S. W.: The Disruption of Abdominal Wounds. Surg. Gynec. Obstet., **72**:1041, 1941.
8. Guiney, E. J., Morris, P. J. and Donaldson, G. A.: Wound Dehiscence. Arch. Surg., **92**:47, 1966.
9. Heughan, C., Niinikoski, J. and Hunt, T. K.: Effect of Excessive Infusion of Saline Solution on Tissue Oxygen Transport. Surg. Gynec. Obstet., **135**:257, 1972.
10. Heughan, C., Zederfeldt, B., Grislis, G. and Hunt, T. K.: Effect of Dextran Solutions on Oxygens Transport in Wound Tissue. Acta Chir. Scand., **138**:639, 1972.
11. Howes, E. L.: The Relationship of the General Condition of the Patient to the Healing of Open Wounds. Internat. Abstr. Surg., **68**:550, 1939.
12. Hugo, N. E., Thompson, L. W., Zook, E. S. and Bennett, J. E.: The Effect of Chronic Anemia on the Tensile Strength of Healing Wounds. Surgery, **66**:741, 1969.
13. Hunt, T. K. and Pai, M. P.: The Effect of Varying Ambient Oxygen Tensions on Wound Metabolism and Collagen Synthesis. Surg. Gynec. Obstet., **135**:561, 1972.
14. Hunt, T. K., Zederfeldt, B., Goldstick, T. K. and Conolly, W. B.: Tissue Oxygen Tensions During Controlled Hemorrhage. Surg. Forum, **18**:3, 1967.
15. Jacobson, M. J. and Van Prohaska, J.: The Healing of Wounds in Iron Deficiency. Surgery, **57**:254, 1965.
16. Juva, K.: Hydroxylation of Proline in the Biosynthesis of Collagen. Acta Physiol. Scand., Supp. 308, 1968.
17. Macon, W. L. and Pories, W. J.: The Effect of Iron Deficiency Anemia on Wound Healing. Surgery, **69**:792, 1971.
18. Mann, L. S., Sprimafola, A. J., Lindesmith, G. G., Levine, M. J. and Kvezerepa, W.: Disruption of Abdominal Wounds, J.A.M.A., **180**:1021, 1962.
19. Marsh, R. C., Coxe, J. W., Ross, W. L. and Stevens, G. A.: Factors Involved in Wound Dehiscence. Survey of 1000 Cases. J.A.M.A., **155**:1197, 1954.
20. Niinikoski, J.: Effect of Oxygen Supply on Wound Healing and Formation of Experimental Granulation Tissue. Acta Physiol. Scand., Supp. 334, 1969.
21. Sandblom, P.: The Tensile Strength of Healing Wounds. Systemic Factors. Anemia and Dehydration. Acta Chir. Scand., **90** (Supp. 89): 71, 1944.
22. Sandberg, N. and Zederfeldt, B.: Influence of Acute Hemorrhage on Wound Healing in the Rabbit. Acta Chir. Scand., **118**:367, 1960.
23. Trueblood, H. W., Nelsen, T. S. and Oberhelman, H. A.: The Effect of Acute Anemia and Non-deficiency Anemia on Wound Healing. Arch. Surg., **99**:113, 1969.
24. Waterman, D. F., Birkhill, F. R., Pirani, C. L. and Levenson, S. M.: The Healing of Wounds in the Presence of Anemia. Surgery, **31**:821, 1952.
25. Whipple, A. C.: The Initial Latent or Lay Period in the Healing of Wounds. Ann. Surg., **112**:481, 1940.
26. Zederfeldt, B.: Studies on Wound Healing and Trauma. Acta Chir. Scand., Suppl. 224, 1957.

The Effect of Dietary Protein Depletion on Immunocompetence:

The Importance of Nutritional Repletion Prior to Immunologic Induction

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MANY SURGICAL PATIENTS are found preoperatively to be malnourished or protein-depleted as a result of sudden starvation secondary to acute conditions of the gastrointestinal tract precluding oral feedings or as a consequence of chronic illnesses such as malignancy, cirrhosis, and inflammatory bowel disease. Studley[18] found that in patients undergoing surgery for peptic ulcers, there was a 33% mortality in those with a preoperative weight loss of over 20% body weight as compared to the 3.5% mortality in those with better nutritional status. Many cases ending in fatalities in this series were attributable to an infectious etiology. Rhoads and Alexander[15] had reported on the increased incidence of post-operative infections in surgical patients with hypoproteinemia.

Although malnutrition seems to increase the susceptibility of the host to infection, the exact relationship between protein depletion and host defense mechanisms is unclear. Previous data in the literature have yielded conflicting results but recent studies in children suggested the presence of depressed humoral and cell-mediated immunity in severe protein-calorie malnutrition.[12,19] Investigations designed to study the association between nutrition and immuno-competence in patients have always been handicapped by the heterogeneity of the patient population, the presence of coexisting infections, the simultaneous presence of vitamin or mineral deficiencies, and the difficulty of precisely quantitating protein-calorie malnutrition.

The advantages of using an animal model to study the problems of malnutrition and immunity lie in the ease of establishing controlled protein-depletion as well as in the absence of coexisting illnesses which may interfere with immunologic assessment. Many past studies in protein-depleted animals have demonstrated impaired antibody production.[4,5,10,13,20] There have also been reports of increased susceptibility of these animals to viral and bacterial infections.[21,22] Some recent work has been done on cellular immune mechanisms but results have been conflicting. The demonstration of impaired thymus-dependent immunity in protein-deficiency states by some investigators[21,23] have been challenged by reports demonstrating enhanced cell-mediated immunity.[11]

Recently Dudrick *et al.* were capable of inducing true weight gain by means of intravenous hyperalimentation in patients with conditions usually associated with significant catabolism.[8,9] The possible advantages of nutritional repletion of the protein depleted surgical patient for purposes of improving immune competence are the ultimate goal of this study. The object of the present study is to use the rat model to evaluate the various immune parameters in chronic protein depletion. A comparison will be made between starting protein

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repletion 48 hrs. before antigenic challenge and starting repletion 48 hrs. after immunization. This will provide valuable information concerning the importance of nutritional status during the inductive early recognition phases of the immune response.

Materials and Methods

A. *Methods of Immunologic Assessment*

1. *Serum Anti-KLH Titration.* KLH (Pacific Biomarine Co., Venice, California) was purified according to the method described by others.[7] Two hundred μg were given to all rats intramuscularly on day zero. Sera were collected at day of sacrifice, 10 days after immunization, for the determination of anti-KLH antibodies using the tanned sheep cell hemagglutination technique.[7]

2. *Spleen Cell Hemolytic Plaque Assay.* Rats were given sheep erythrocytes according to the protocol described below. Spleens were collected from rats at time of sacrifice, in chilled medium-199 (Microbiological Assoc., Bethesda, Md.). Spleens were cut into small fragments and cell suspensions were prepared by passage of fragments through size 50 wire mesh. Lymphoid cells were counted. The direct plaque assay for IgM producing cells was then performed exactly as described earlier by us.[2] For the development of the indirect IgG hemolytic plaques, 1 ml of 1:100 dilution of goat anti-rat globulin (Hyland Laboratories, California) was added to the plates at time of plating the cells and then allowed to incubate for one hour prior to addition of the guinea pig complement.

3. *In Vitro Lymphocyte Response to Mitogens.* At the time of sacrifice, cervical lymph nodes were collected in medium 199, using a sterile technique. Cell suspensions were prepared by passage of nodes through sterile No. 50 wire mesh. Cell counts were then done and cell suspensions were adjusted to contain 2 × 10^6 lymphocytes/ml. The technique of *in vitro* cell culture was as described earlier by us.[1] In all cases 10% fetal serum was used.

B. *Animal Groups*

7–15 week-old female Sprague-Dawley rats (Charles River, Wilmington, Mass.) weighing 150–350 grams were used for this study. The animals were housed in group cages, fed water and either normal rat chow or protein-free diet ad libitum. Rats were divided into 4 groups in such a way that the mean weights would be approximately equal after potein depletion. Protein-depleted rats were those that were maintained on a protein-free diet for six weeks before initiating the studies.

All animals followed the same protocol for immunologic evaluation. At day 0, each rat was given 0.2 or 2.0 mg KLH intramuscularly, 0.1 ml complete Freund's adjuvant intradermally in the foot pad, and 1 × 10^8 sheep erythrocytes were injected intraperitonially. On day 2, 0.5 ×10^8 sheep erythrocytes were re-injected. On day 9, animals were skin tested with 50 μg PPD intradermally. Skin tests were read 24 hours later and animals were then sacrificed. Sera, spleens and lymph nodes were obtained as described.

A total of 127 rats were studied and these were divided into the following four groups according to diet schedule:

I. Normal: maintained on regular rat chow (Wayne-Lab Blox, General Biochemicals, Chagrin Falls, Ohio).

II. Depleted: this group was protein-depleted for 6 weeks before immunizations and was continued on the protein-free diet (Biological Research Products Mod. Cat. #170590, Chagrin Falls, Ohio) until sacrificed. In this diet, protein has been replaced isocalorically with corn starch.

III. Repleted A: this group was protein-depleted for 6 weeks but was repleted using the regular rat chow 48 hrs. before immunizations. They were maintained on the regular diet until sacrificed.

IV. Repleted B: this group was protein depleted for 6 weeks but was refed a regular diet 48 hrs. after immunizations until sacrificed.

To quantitate the degree of protein depletion and repletion, weights at various times were recorded. Re-

TABLE 1. *Weights at Various Times of Study*

Group	No. Rats Studied	Mean Initial Wt. (gm) (Mean & Range)	Mean Wt. (gm) after Protein Depletion (Mean & Range)	% Wt. Loss	Mean Wt. (gm) Gain During Repletion	Mean Wt. (gm) on Day of Sacrifice (Mean & Range)
Normal	40	191 (160–333)	—	—	—	219 (175–331)
Depleted	30	253 (178–370)	174 (111–277)	31%	—	163 (104–253)
Repleted A*	30	232 (187–286)	160 (132–194)	32%	84	244 (204–286)
Repleted B†	27	248 (201–336)	173 (142–258)	31%	69	242 (211–325)

* Protein depleted rats that were started back on regular rat chow 48 hrs *prior* to sensitization

† Protein depleted rats that were started back on regular rat chow 48 hrs *after* sensitization

sults are found in Table 1. The normal group of rats had a mean weight gain of 28 gms during the 10 day period of experimentation. The depleted group had a mean initial weight of 253 gms and had a mean weight of 163 gms at the time of sacrifice. This represents an average weight loss of 31%. The group designated repleted-A had an initial weight of 232 gms, and experienced a 32% weight loss during the 6-week period of protein restriction. Their mean weight gain during the 12 day period of protein repletion before their sacrifice was 84 gms. Repleted group B had an initial weight of 248 gms, and lost 31% of their initial weight. Their mean weight gain during the 8 days of protein repletion was 69 gms. (Table 1).

Results

Anti-KLH Titers (Table 2)

Anti-KLH titers in depleted animals failed to show a significantly depressed response, less than 2 tubes dilution difference, compared to normals. A subnormal response is suggested, however, with both antigenic doses. The highest titers were recorded in the group repleted 48 hrs. prior to immunization and antibody titers at both sensitizing doses were significantly different from titers of the depleted group ($p < 0.02$). The anti-KLH response of repleted group B is comparable to that of normals. Titers of the depleted group or the repleted group B were not significantly different from the normal group ($p > 0.05$).

Hemolytic Spleen Plaque Assay (Table 3)

Protein-depleted rats were shown to have mean direct and indirect plaque counts per spleen only approximately half that of normals. The animals which were protein repleted 48 hrs. prior to antigenic stimulation, however, demonstrated twice normal values of IgM producing cells and almost 3 times normal IgG producing cells. Repleted group B showed a near normal response. When plaque counts were calculated on the basis of 10^6 lymphoid cells plated instead of per spleen, depression was not demonstrated in the depleted group although twice normal response was still evident in repleted group A.

TABLE 2. *Primary Sensitization with Keyhole Limpet Hemocyanin (KLH)*

	Anti-KLH Titres† Following Sensitization with KLH‡			
Group Tested	2.0 mg Mean§ & Range	No. of Rats Tested	0.2 mg Mean§ & Range	No. of Rats Tested
Normal	64(64–128)	11	8(1–20)	10
Depleted	32(4–128)	8	4(1–10)	8
Repleted A*	128(32–256)	16	16(10–40)	9
Repleted B*	64(16–256)	13	8(1–10)	8

* Depleted rats that were repleted 2 days before (Group A) or 2 days after (Group B) primary sensitization.

† Reciprocal of hemagglutination titers × 10^3.

‡ Rats were injected with either 0.2 mg or 2.0 mg KLH i.m. 10 days before determination of serum anti-KLH titers.

§ Geometric mean titers.

PPD Skin Tests (Table 4)

Skin test results demonstrated that the highest percentage of positive skin tests was in the group repleted 48 hrs. prior to injection of complete Freunds' adjuvant and the lowest percentage was in the depleted group. Only 5% of depleted animals showed a skin induration > 10 mm compared to 23% of the normal controls and 48% of repleted group A. If the criteria for positive skin test were changed to > 5 mm, the relative percentages in the 4 groups become 67, 5, 95 and 47 as shown in Table 4.

In Vitro Lymphocyte Proliferation (Table 4)

The mean specific incorporation (S. I.) of tritiated thymidine by lymph node lymphocytes from normal rats in response to 0.1 ml of 1:10 dilution of phytohemagglutinin-M (PHA) was 5.9 compared to 2.2 of the depleted group. Repleted group A and repleted group B showed S.I. of 8.3, and 4.7 respectively. With a larger amount of PHA (0.3 ml) added to the cell culture, the highest mean S.I. of 18.4 was again recorded in repleted group A which had received 12 days of nutritional repletion. Normal and depleted groups responded with specific incorporations of 9.2 and 3.9 respectively. Repleted group B which had received 8 days of protein repletion before the lymphocytes were cultured yielded an intermediate response with a S.I. of 7.4. Lymphocyte stimulation with pokeweed mitogen demonstrated a mean S.I. of 5.6 for the normal group as compared with 1.2 of the depleted group. Repleted group A and B had mean S.I. of 5.8 and 3.8 respectively.

Discussion

Evaluation of the bone marrow dependent system in this study was accomplished by hemolytic splenic plaque assays, measurements of anti-KLH antibodies, and assessment of *in vitro* lymphocyte proliferation in response to pokeweed mitogen. Thymus-dependent immune response was evaluated by the use of PPD skin tests and *in vitro* lymphocyte proliferation in response to phytohemagglutinin. Results indicate impairment of both B and T cell immunity in rats which have lost approximately 30% of their body weight over a 6-week period via dietary protein restriction. More importantly, this study demonstrates that adequate nutritional status is important for the successful induction of the immune response. Animals which were started on protein repletion 48 hrs. before immunologic challenge showed supernormal immune responses. However, animals which were sensitized at a depleted state and repleted 48 hrs.

TABLE 3. *Hemolytic Splenic Plaque Assay Following Immunization with Sheep Erythrocytes*

Group	Number of Plaques (Mean & Range)† Per Spleen Direct (× 10³)‡	Per Spleen Indirect (× 10³)‡	Per 10⁶ Lymphoid Cells Plated Direct‡	Per 10⁶ Lymphoid Cells Plated Indirect‡	Mean # of Lymphoid Cells ×10⁶ Per Spleen (Mean & Range)
Normal	6.6(1.7–13.5) [7]	5.0(3.5–7.8) [4]	12.7(7–25) [7]	11.7(6–20) [4]	531(330–750)
Depleted	2.5(1.0–4.4) [9]	2.6(1.0–4.2) [4]	16.6(6–33) [9]	14.0(11–19) [4]	166(90–300)
Repleted (A)*	12.5(4.5–20.4) [5]	14.5(10.3–22.3) [3]	24.4(15–40) [5]	25.0(20–31) [3]	498(300–720)
Repleted (B)*	5.7(1.7–12.9) [6]	8.3(0–13.0) [4]	11.3(1–25) [6]	13.7(0–23) [4]	525(270–900)

* Depleted rats that were repleted two days before (Group A) or two days after (Group B) the first intraperitoneal administration of sheep erythrocytes (day 0).

† Rats were given 1 × 10^8 & 0.5 × 10^8 erythrocytes on days 0 & 2 respectively. All rats were sacrificed for the plaque assay on day 10 Numbers between [ ] represent numbers of rats tested.

‡ Direct and indirect represent number of plaques in absence of or presence of goat anti-rat immunoglobulin antiserum respectively.

later demonstrated a partial improvement in their immune responses.

Many studies in the past have demonstrated impaired antibody production in protein-depleted rats, mice, and rabbits.[4,5,10,13,20] The repletion of malnourished animals with optimal diets have been shown to reverse the increased susceptibility to viral or bacterial infection observed during malnutrition[21,22] while improvement of antibody production has also been seen after successful protein repletion of previously depleted animals.[10,20] Kenney *et al.* have recently demonstrated that protein malnutrition in adult Wistar rats is associated with smaller spleens with less nitrogen and RNA.[13] Using the method of hemolytic spleen plaque assay, we have demonstrated in this study that the total number of antibody-forming cells in depleted animals was only one-third of normal, but antibody production per a fixed number of lymphoid spleen cells was not decreased. This would indicate that the defect is due to a decreased number of lymphoid cell and not due to failure of the antibody forming cell to secrete antibodies. It seems that malnutrition depleted both the IgM and IgG producing cells.

In this study, B cell mediated immune function as demonstrated by serum anti-KLH titer following sensitization was also evaluated. We were able to demonstrate a depression of the anti-KLH titers in the depleted group, though the difference in the titer was not significantly different from that of the control normal group. We considered 2 dilutions difference in the geometric mean titer to be significant.

The recent studies of thymus dependent function (cell-mediated immunity) in malnourished animals have yielded interesting and conflicting results. Atrophy of lymphoid tissue and thymus gland in marasmic mice was evident in studies of Woodruff,[21,22] and this was shown to be reversible by conversion to an optimum diet for one month. In addition, the increased susceptibility of marasmic mice to Coxsackie virus B_3 infection can be reduced by transfer of lymphoid cells from healthy mice

TABLE 4. *PPD Skin Tests and In Vitro Proliferative Response of Lymph Node Lymphocytes to Phytomitogens*

Group	% of Rats with Positive Skin Test† [No. Tested] 10 mm	5 mm	Specific Incorporation‡ in Presence of (Mean and Ranges) & [No. Tested] PHA 1:10 (0.1 ml)	PHA 1:10 (0.3 ml)	PWM 1:10 (0.1 ml)
Normal	23 [27]	67 [27]	5.9 (0.3–21.7) [17]	9.2 (4.4–12.3) [7]	5.6 (0.7–13.2) [12]
Depleted	5 [20]	5 [20]	2.2 (0.5–6.4) [11]	3.9 (0.6–9.9) [9]	1.2 (0.6–2.9) [5]
Repleted A*	48 [21]	95 [21]	8.3 (0.7–28.6) [6]	18.4 (0.9–43.9) [6]	5.8 (0.6–13.9) [6]
Repleted B*	32 [19]	47 [19]	4.7 (1.2–11.9) [6]	7.4 (1.7–20.3) [6]	3.8 (0.8–8.8) [6]

* Depleted rats that were repleted two days before (Group A) or two days after (Group B) primary sensitization.

† Rats were injected with 0.1 ml complete Freunds' adjuvant and tested with 50 μg PPD ID 9 days later.

‡ Specific incorporation is the ratio of counts/min (cpm) of three days cell cultures to which the phytomitogen was added to cpm of cultures to which no mitogen was added (control cutlures). The latter cultures gave 169 (92–312) cpm. Means, ranges, and no. of experiments from different rats are shown.

recovering from infection.[23] Other authors,[11] however, have claimed that protein deficiency may enhance cell-mediated immunity as demonstrated by enhanced graft rejection. In this study thymus dependent function was assessed by delayed skin reactivity to tuberculoprotein and by the *in vitro* lymphocyte responses to PHA and was found to be suppressed in protein malnutrition. The enhanced T-cell function demonstrated by others[11] in malnutrition was thought to be due to a depressed production of a blocking antibody.

A significant finding in this study is the supranormal response recorded in every immune parameter studied in the group of animals (Group A) protein-repleted 48 hrs. prior to sensitization (Tables 2–4). Rats (Group B) which received protein repletion 48 hrs. after sensitization demonstrated only near-normal immunocompetence. This significant difference in the magnitude of the response between repleted Group A and B indicates that nutritional status during the induction and/or proliferative phase of the immune response is crucial, and points to the immunologic advantage of early nutritional repletion. The rebound type of supranormal response recorded in repleted Group A is apparently not unique to our study model. Supranormal rates of hepatocyte synthesis of albumin have been observed during early protein repletion of previously depleted animals.[14,17]

Despite the wide use of modern antibiotics in recent years, it is evident that satisfactory prevention and treatment of infections in surgical patients have not been attained.[3] Better understanding of host defense mechanisms and factors which alter them can provide new insights to the problems of infections in the surgical patient. Data from this study and those of others[4,5,10,12,13,19,20] demonstrate that nutritional status is one of the determinants of host immuno-competence and the recognition that malnourished patients have poor host defenses is important in surgical practice.

Malnutrition is commonly observed in many patients on a surgical service. Oral feedings are denied to patients with bowel fistulae and those with prolonged intestinal obstruction or ileus. Patients with severe trauma or burns and those on respirators or with depressed central nervous system function are also unable to feed by mouth for long periods. In addition, necessary surgical intervention in some of these already malnourished patients can represent a further metabolic insult. The recognition that protein malnutrition is associated with impaired host defense mechanisms therefore urges adequate nutritional therapy in surgical patients both pre-and post-operatively. Improvement of patients' immunocompetence may yield improved surgical morbidity and mortality. In patients whose conditions preclude the effective use of the gastrointestinal tract for feeding, the use of total parenteral hyperalimentation should be considered.[8,9] Data from this study would also suggest that early or prophylactic nutritional repletion may be more beneficial as it would permit successful immunologic induction upon antigenic challenge.

There have been many reports of infectious complications, especially fungal, in patients receiving parenteral nutrition.[6] This could be one of the manifestations of depressed cellular immunity in patients with poor nutritional status but does not really constitute a contraindication to intravenous hyperalimentation. Meticulous care of the subclavian catheter, the catheter site, and nutritional solutions will ensure that severe infectious complications are rare even in depressed hosts. The proper use of parenteral hyperalimentation or other means of nutritional therapy can theoretically break the vicious cycle of malnutrition and infection and equip the patient with optimal host defense mechanisms.

Summary

The use of serum anti-KLH antibody assay, the hemolytic spleen plaque assays, delayed skin tests to tuberculin, and in vitro lymphocyte transformation in response to mitogens, have demonstrated the depression of humoral and cell-mediated immunity in young adult rats who were protein-depleted by being fed protein-free diet for 6 weeks. Protein repletion of the protein depleted rats 48 hrs. before antigen administration resulted in significant supranormal responses in all immune parameters tested. Those animals whose repletion started 48 hrs. after sensitization still demonstrated subnormal responses. It is concluded that nutritional status during the induction and/or proliferative phase of the immune response is important for the full expression of the immune response.

Malnutrition, a frequent finding among surgical patients, may be responsible for increased susceptibility to infection and early prophylactic nutritional repletion may have a vital role in restoring immune competence. In many surgical patients whose conditions preclude the use of the gastrointestinal tract for feeding, the use of intravenous hyperalimentation deserves special consideration.

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References

1. Abdou, N. I.: Immunoglobulin Receptors on Human Peripheral Leukocytes II Class Restriction of Ig Receptors. J. Immunol., **107**:1637, 1971.
2. Abdou, N. I. and Richter, M.: Cells Involved in the Immune Response. VI The Immune Response to Red Blood Cells in Irradiated Rabbits Following Administration of Normal,

Primed or Immune Allogeneic Rabbit Bone Marrow Cells. J. Exp. Med., **129**:757, 1969.

3. Altemeier, W. A.: The Significance of Infection in Trauma. Bull. Am. Coll. Surg., **57**:7, 1972.
4. Cannon, P. R., Chase, W. E. and Wissler, R. W.: The Relationship of the Protein Reserves to Antibody Production. J. Immunol., **47**:133, 1943.
5. Cannon, P. R., Wissler, R. W., Woolridge, R. L. and Benditt, E. P.: The Relationship of Protein Deficiency to Surgical Infection. Ann. Surg., **120**:514, 1944.
6. Curry, C. R. and Quie, P. G.: Fungal Septicemia in Patients Receiving Parenteral Hyperalimentation. New Engl. J. Med., **285**:1221, 1971.
7. Curtis, J. E., Hersh, E. M., Butler, W. T. and Rossen, R. D.: Antigen Dose in the Immune Response. J. Lab. and Clin. Med., **78**:61, 1971.
8. Dudrick, S. J., Long, J. M., Steiger, E. and Rhoads, J. E.: Intravenous Hyperalimentation. Med. Clin. N. Amer., **54**: 577, 1970.
9. Dudrick, S. J., Wilmore, D. W. Vars, H. M. and Rhoads, J. E.: Can Intravenous Feeding as the Sole Means of Nutrition Support Growth in the Child and Restore Weight Loss in an Adult? Ann. Surg., **169**:974, 1969.
10. Gemeroy, D. G. and Koffler, A. H.: The Production of Antibodies in Protein Depleted and Repleted Rabbits. J. Nutr., **39**:299, 1949.
11. Jose, D. G. and Good, R. A.: Absence of Enhancing Antibody in Cell-Mediated Immunity to Tumor Heterografts in Protein Deficient Rats. Nature, 231:323, 1971.
12. Jose, D. G., Welch, J. S. and Doherty, R. L.: Humoral and Cellular Immune Responses to Streptococcal, Influenza, and Other Antigens in Australian Aboriginal School Children. Aust. Pediat. J., **6**:192, 1970.
13. Kenney, M. A., Roderuck, C. E., Arnrich, L. and Piedad, F.: Effects of Protein Deficiency on the Spleen and Antibody Formation in Rats. J. Nutr., **95**:173, 1968.
14. Kirsch, R., Frith, L., Black, E. and Hoffenberg, R.: Regulation of Albumin Synthesis and Catabolism by Alteration of Dietary Protein. Nature, **217**:579, 1968.
15. Rhoads, J. E. and Alexander, C. E.: Nutritional Problems of Surgical Patients. Ann. N. Y. Acad. Sci., **63**:268, 1955.
16. Rodey, G. E. and Good, R. A.: The In Vitro Response to Phytohemagglutinin of Lymphoid Cells from Normal and Neonatally Thymectomized Adult Mice. Int. Arch. Allergy, **36**:399, 1969.
17. Rothschild, M. A., Oratz, M., Mongelli, J. and Schreiber, S. S.: Effects of a Short-Term Fast on Albumin Synthesis Studied In Vivo, in the Perfused Liver, and on Amino Acid Incorporation by Hepatic Microsomes. J. Clin. Inves., **47**:2591, 1968.
18. Studley, H. O.: Percentage of Weight Loss. A Basic Indicator of Surgical Risk in Patients with Chronic Peptic Ulcer. J.A.M.A., **106**:458, 1936.
19. Smythe, P. M., Schonland, M., Brereton-Stiles, G. G., Coovadia, H. M., Grace, H. J., Loening, W. E. K., Mafoyane, A., Parent, M. A. and Vos, G. H.: Thymolymphatic Deficiency and Depression of Cell-Mediated Immunity in Protein-Calorie Malnutrition. Lancet, **2**:939, 1971.
20. Wissler, R. W., Woolridge, R. L., Steffee, C. H., Jr. and Cannon, P. R.: The Relationship of the Protein-Reserves to Antibody Production. II. The Influence of Protein-Repletion Upon the Production of Antibody in Hypoproteinemic Adult White Rats. J. Immunol., **52**:267, 1946.
21. Woodruff, J. F.: The Influence of Quantitated Post-Weaning Undernutrition in Coxsackievirus B_3 Infection of Adult Mice. II Alteration of Host Defense Mechanisms. J. Infect. Dis., **121**:164, 1969.
22. Woodruff, J. F. and Kilbourne, E. D.: The Influence of Quantitated Post-Weaning Undernutrition on Coxsackievirus B_3 Infection of Adult Mice. I Viral Persistence and Increased Severity of Lesions. J. Infect. Dis., **121**:137, 1969.
23. Woodruff, J. F. and Woodruff, J. J.: Modification of Severe Coxsackievirus B_3 Infection in Marasmic Mice by Transfer of Immune Lymphoid Cells. Proc. Nat. Acad. Sci., **68**:2108, 1971.

Meat Extract-Stimulated Gastric Acid Secretion Before and After Parietal Cell Vagotomy without Antrum Drainage and Selective Gastric Vagotomy with Drainage in Patients with Duodenal Ulcer

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AFTER PARIETAL CELL VAGOTOMY (PCV) the parietal cell mass of the stomach is denervated, while the antrum is left innervated and without drainage. While the insulin stimulated acid secretion often disappears and the stomach emptying is normal after PCV in dogs,[1] this operation results in an enhanced acid response to feeding and in an approximately 50% increase of the 24-hour Heidenheim Pouch (HP) acid secretion.[1,3] In the normal dog the HP acid response to feeding can be substantially decreased, but not eliminated by denervating the antrum.[6] A similar decrease can be observed when a PCV in the dog is supplemented with a suprapyloric antrectomy or a suprapyloric mucosal antrectomy.[2] These experiments suggest that vagal innervation increases the antral response to food, and that in the absence of acid inhibition, antral secretion of gastrin is not only present, but may be increased. The clinical significance of a possible enhanced acid response to feeding in duodenal ulcer patients treated by a PCV[5,10] is not known.

This study was therefore performed to evaluate acid response to meat extract in duodenal ulcer patients before and after PCV or selective gastric vagotomy with antral drainage (SV + P), after which operation the whole of the stomach is denervated and the antrum drained by a pyloroplasty or a gastroduodenostomy.[4] Furthermore, the study determines the covariation of meat extract stimulated acid secretion with fasting, basal, insulin and pentapeptide stimulated acid secretion in the same patients.

Material and Method

Twenty-five patients (4 females and 21 males, mean age 56 years (range 27–76)) underwent surgery for duodenal ulcer complaints. At operation a duodenal or pyloric niche was found in 17 patients, duodenal or pyloric ulcer scarring in 7 patients and no ulcer in *one* patient. In 19 patients with no pyloric stenosis PCV, and in 6 patients with pyloric stenosis of varying degree SV + P were performed.

Gastric secretion studies were carried out preoperatively and between two and three month postoperatively. The *pentapeptide test* was performed by stimulation with 6 microgram Peptavlon (ICI)/kg s.c. before the operation (25 patients) and with 10 microgram Peptavlon/kg s.c. after the operation (19 patients).

The doses of 6 and 10 microgram Peptavlon have previously been shown to elicit maximal acid output both before and after PCV.[11] The *insulin test* was performed by stimulation with 0.2 I.U./kg i.v. in 12 patients before and in 22 patients after operation. The *meat extract test* was done in 25 patients before and in 21 patients after operation, only slightly modified after Giles and Clark.[8] Three oxo cubes* were dissolved in 200 ml warm water

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* Containing protein: 1.62 g, fat: 0.58 g, carbohydrate: 204 g.

and pH adjusted to 7.0 by adding 15–20 ml of 8% sodium bicarbonate. This solution was introduced into the stomach via the tube and left in the stomach 15 minutes with the patient in a sitting position. The stomach was then emptied by 5 minutes aspiration with the patient supine. The stomach was then rinsed by 200 ml of water and emptied by a further 5 minutes aspiration, the entire procedure of meat extract stimulation lasting about 30 minutes.

All tests were done after an overnight fast. Gastric tubes were placed under fluoroscopic control with the patients supine. Aspiration was performed by intermittent pump suction, which was constantly supervised; aspirates were collected every 15 minutes. The first 15-minute aspirate obtained before meat extract stimulation is designated "fasting secretion" and the total of the next 4 15-minute aspirates (which were analyzed separately) is designated "basal secretion."

After pentapeptide and meat extract stimulation, 6 15-minutes aspirates were collected and after insulin there were 9 15-minutes aspirate collections. For each aspirate over the 15-minutes periods volume, pH (Radiometer) and acidity (by titration to pH 3.5) were measured. Maximal acid production is expressed as "peak acid output" (PAO), the highest acid production in two consecutive 15-minutes periods multiplied by two (meq/hr.) and as acid production during the first hour after stimulation (meq/hr.). There was undoubtedly some loss of acid secretion, especially after SV + P, but no attempt was made to correct for this.

Statistical Calculations

The covariations were evaluated by Spearman's coefficient of correlation (r_{Sp}). The p-values were obtained from Documenta Geigy.

Results

Before operation all patients responded to meat extract with a significantly ($p < 0.001$) increased acid secretion. PAO-meat extract averaged 60% of PAO-pentapeptide (Table 1, Fig. 1). There was a statistically significant positive correlation between PAO-meat extract and fasting acid secretion ($p < 0.01$), basal acid output ($p < 0.01$), and especially fasting volume ($p < 0.001$) and PAO-pentapeptide ($p < 0.001$) (Table 1). There was no correlation to PAO-insulin in 12 patients.

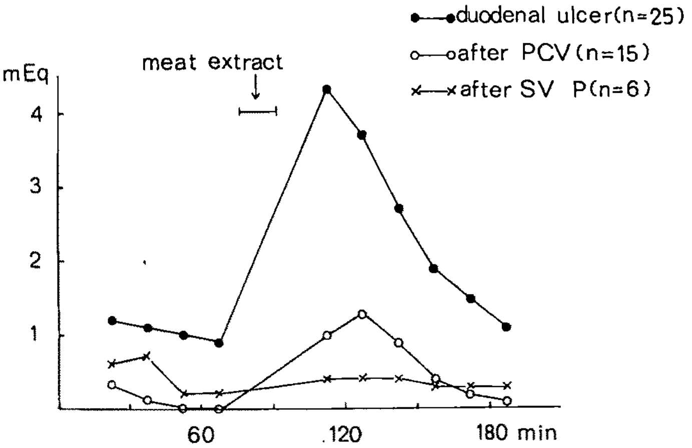

FIG. 1. Meat extract activated acid secretion during basal hour and the first hour after stimulation before and after PCV and SV + P in patients with duodenal ulcer.

After operation there was still a highly significant ($p < 0.001$), but less pronounced ($r_{Sp} = 0.58$) positive correlation between the fasting volume and PAO-meat extract (Table 2).

No free acid in fasting and/or basal secretion was found in 15 patients and no correlation with PAO-meat extract was present (Table 2).

While the entire instilled amount of meat extract usually could be recovered preoperatively, this was after operation only the case in 7 patients, all of whom had a PCV. In the remaining 14 patients only about half of the instilled amount could be obtained by aspiration.

After operation PAO-meat extract was significantly ($p < 0.02$) but less pronounced ($r_{Sp} = 0.58$) correlated positive with PAO-pentapeptide. The acid response to meat extract was significantly decreased, and PAO-meat extract averaged only 37% of simultaneous PAO-pentapeptide (Table 2, Fig. 1), because the mean postoperative reduction was respectively 71% (PAO-meat extract) and 52% (PAO-pentapeptide) (Table 3). A significant covariation ($r_{Sp} = 0.62$, $p_{Sp} < 0.02$) of reduction of PAO-meat extract with PAO-pentapeptide could be demonstrated only in insulin-negative patients ($n = 12$),[9] while reductions of PAO-meat extract was much more pronounced than reductions of PAO-pentapeptide in insulin-positive patients ($n = 7$) (Table 3).

If more acid secretion during the first hour after stimulation than during the basal hour is taken as evidence

TABLE 1. *Preoperative Acid Tests (mean ± sd) in 25 Patients with Duodenal Ulcer*

	Fasting Volume ml	Fasting Acid Secretion mEq/15 min.	Basal Acid Secretion mEq/hr.	PAO-pentapeptide mEq/hr.	PAO-insulin mEq/hr.	PAO-meat extract mEq/hr.
	96 ± 41	1.8 ± 1.7	4.5 ± 4.4	28.1 ± 10.7	27.3 ± 10.3	16.9 ± 8.8
Correlation (r_{Sp}) to PAO-meat Extract	0.67 ($P_{Sp} < 0.001$)	0.59 ($P_{Sp} < 0.01$)	0.58 ($P_{Sp} < 0.01$)	0.88 ($P_{Sp} < 0.001$)	No correlation	

TABLE 2. *Postoperative Acid Tests (mean ± sd) in Patients with Duodenal Ulcer*

	Fasting Volume ml	Fasting Acid Secretion mEq/15 min.	Basal Acid Secretion mEq/hr.	PAO-pentapeptide mEq/hr.	PAO-insulin mEq/hr.	PAO-meat extract mEq/hr.
	72 ± 43	0.7	0.7	12.1 ± 8.2	1.5	4.4 ± 4.7
		(range: 0–6.4)	(range: 0–7.5)		(range: 0–5.6)	
	(n = 21)	(n = 21)	(n = 21)	(n = 19)	(n = 22)	(n = 21)
Correlation (r_{Sp}) to PAO-meat Extract	0.58 ($P_{Sp} < 0.001$)	No correlation	No correlation	0.58 ($P_{Sp} < 0.02$)	0.45 ($P_{Sp} < 0.05$)	

of meat extract stimulation, this was found in 11 of 15 patients after PCV and in none of the 6 patients after SV + P (Table 3, Fig. 1). This difference is statistically significant ($p < 0.05$).

Discussion

Meat extract is a potent activator of acid secretion in patients with duodenal ulcer, confirming previous data.[8,10,15]

Before operation, the amount of fasting gastric juice is positively and significantly correlated to meat extract stimulated acid secretion, which is, furthermore, positively correlated to the fasting, basal and, especially, the pentapeptide activated gastric acid secretion.

Significant changes of acid secretion takes place *after PCV and SV + P*; fasting, basal, insulin and pentapeptide stimulated acid secretion is reduced in same extent as previously reported in larger series.[12,13] The average reduction of PAO-meat extract is 71% and still positively correlated with the amount of fasting gastric juice. The fact that patients with the smallest amount of fasting juice have the lowest PAO-meat extract is well in accordance with the observation, that meat extract-stimulated serum gastrin response is twice as great after PCV (with more normal gastric emptying) than after PCV + pyloroplasty (with a significant more rapid gastric emptying).[7] Both observations indicate that a fast gastric emptying reduces both the amount of fasting gastric juice and the meat extract stimulated secretion of gastrin and acid.

TABLE 3. *Gastric Acid Secretion 2–3 Months after Parietal Cell Vagotomy and Selective Vagotomy with Pyloroplasty*

Patient No.	Basal Acid Secretion mEq/hr.	Acid Secretion One Hour after Meat Extract mEq/hr.	Postoperative Reduction of PAO-pentapeptide Per Cent	PAO-meat extract Per Cent
After PVC Insulin − ve				
7.615	0	0	—	—
24.809	0	3.7	69	71
25.326	0	8.1	60	63
25.728	0	3.2	−63	− 25
25.746	0	4.8	38	24
25.868	0	9.8	67	41
25.947	0	0.1	88	97
26.076	0	0	61	100
26.422	0.4	6.1	39	58
26.498	0	0	78	100
20.860 (No Insulin test)	0	4.3	—	—
After PCV Insulin + ve				
25.730 (late+ve)	0.2	1.5	29	89
26.158 (late+ve)	0.1	1.1	20	88
26.160 (early+ve)	0	1.9	43	65
26.402 (early+ve)	4.5	9.8	43	57
After SV + P Insulin − ve				
24.776	0	0	84	100
25.646	0.7	0	86	98
26.012	0.2	0	55	100
After SV + P Insulin + ve				
25.643 (late+ve)	0	0	63	100
25.682 (late+ve)	2.0	0.4	64	73
26.543 (late+ve)	7.5	7.7	69	54

After PCV, 11 of 15 patients demonstrated a low, but significant meat extract-stimulated acid secretion. During the first hour after stimulation an average of 3.6 meq of acid is produced ($n = 15$). The average reduction of PAO-meat extract is 64% ($n = 13$). This reduction is greater than the simultaneous reduction of PAO-pentapeptide, which in the same patients was 44%. In patients after PCV, gastric emptying is normal, the antrum is innervated and reduction of PAO-meat extract is positively correlated with reduction of PAO-pentapeptide in patients with complete vagotomy. This shows that meat extract stimulates the innervated and motorically normal functioning antrum, but to a much lesser degree than before operation. This in turn indicates that in man, complete denervation of the parietal cell mass, not denervation of the antrum, is the chief cause of the reduced acid response to meat extract.

In contrast to the secretory pattern after PCV, no meat extract-stimulated acid secretion was found after SV + P. This complete elimination of acid secretion can be caused either by different pattern of gastric emptying after the two operations or by antral denervation, which is included in SV:

Gastric emptying is normal or slightly increased after PCV. In contrast significantly increased gastric emptying is often seen after SV +P under which circumstances food remains in the antrum for too brief a time for it to be activated. An exact evaluation of the influence of gastric emptying on meat extract stimulation can, anyway, only be done by assessing recovery after marking the instilled meat extract. It is noteworthy that in this series recovery of the entire amount of instilled meat extract was only found after PCV.

The role of antral denervation on reduction of meat extract-stimulated acid secretion, is difficult to evaluate. Meat extract acid secretion is nil or sparse in patients with antral denervation after complete (insulin-negative) truncal vagotomy and pyloroplasty[8,10,15] and after SV + P, as shown in this study. The significant meat extract stimulation in patients with intact antral innervation after PCV and in patients with incomplete (insulin-positive) truncal vagotomy and pyloroplasty[15] seems to indicate that innervation of the antrum is necessary for the acid response to feeding with meat extract.

Conclusion

After PCV a significant meat extract-stimulated acid secretion is to be expected. It is generated either by normal gastric emptying or the presence of an innervated antrum. In comparison with the preoperative acid pattern the postoperative meat extract activated acid secretion is greatly reduced, and is correlated with a positive pentapeptide response. No response is seen in patients following selective vagotomy and antral drainage. It is too early to state whether persistance of stimulated acid secretion following parietal cell vagotomy will result in a higher recurrence rate in operations for duodenal ulcer.

Summary

Meat extract is a potent activator of gastric acid secretion in 25 patients with duodenal ulcer. Maximal acid secretion after meat extract stimulation is positively correlated to the amount of fasting gastric juice, fasting and basal acid output, and especially pentapeptide activated acid secretion.

Meat extract is a poor activator of gastric acid secretion after parietal cell vagotomy and after selective vagotomy and pyloroplasty. Maximal acid secretion after meat extract stimulation retains only a positive correlation with the amount of fasting gastric juice and with pentapeptide activated acid secretion.

Significant, but greatly reduced, meat extract-stimulated acid secretion is found in 11 of 15 patients after parietal cell vagotomy. The postoperative reduction of maximal acid output after meat extract is positively correlated to the reduction of pentapeptide stimulated acid secretion in patients with complete (insulin-negative) parietal cell vagotomy.

Meat extract-stimulated acid secretion is eliminated in 6 patients after selective gastric vagotomy and pyloroplasty.

The difference of secretory pattern after the two operations is significant and the possible influence of antral denervation and gastric emptying on these results is discussed.

Acknowledgment

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References

1. Amdrup, B. M. and Griffith, C. A.: Selective Vagotomy of the Parietal Cell Mass: Part I: With Preservation of the Innervated Antrum and Pylorus. Ann. Surg., 170:207, 1969.
2. Amdrup, B. M. and Griffith, C. A.: Selective Vagotomy of the Parietal Cell Mass: Part II: With Suprapyloric Mucosal Antrectomy and Suprapyloric Antral Resection. Ann. Surg., 170:215, 1969.
3. Amdrup, B. M. and Griffith, C. A.: The Effect of Insulin upon the Secretory Response to Feeding in Dogs with Selective Vagotomy of the Parietal Cell Mass. Scand. J. Gastroent., 5:655, 1971.
4. Amdrup, E., Clemmesen, T. and Andreassen, J.: Selective Gastric Vagotomy Technic and Primary Results. Amer. J. Dig. Dis., 12:351, 1967.
5. Amdrup, E. and Jensen, H.-E.: Selective Vagotomy of the Parietal Cell Mass Preserving Innervation of the Undrained Antrum. Gastroenterology, 59:522, 1970.

6. Castella, H. de and Irvine, W. T.: The Role of the Vagus in the Antral Response to Food. Brit. J. Surg., **54**:828, 1967.
7. Clarke, R. J., Jaffe, B. M., Clendinnen, B. J. and Williams, J. A.: Is a Pyloroplasty Necessary with Proximal Gastric Vagotomy? Brit. Soc. Gastroenterology, 33rd General Meeting, Aviemore 1972. p. 22–23.
8. Giles, G. R. and Clark, C. G.: Gastric Secretion Stimulated by Meat Extract in Man. A Test of Antral Function: Scand. J. Gastroent., **1**:159, 1966.
9. Hollander, F.: Laboratory Procedures in the Study of Vagotomy (With Particular Reference to the Insulin Test). Gastroenterology, **11**:419, 1948.
10. Johnston, D. and Wilkinson, A. R.: Highly Selective Vagotomy without a Drainage Procedure in the Treatment of Duodenal Ulcer. Brit. J. Surg., **57**:289, 1970.
11. Johnston, D., Wilkinson, A. R., Humphrey, C. S., Smith, R. B., Goligher, J. C., Kragelund, E. and Amdrup, E.: Serial Studies of Gastric Secretion in Patients after Highly Selective (Parietal-cell) Vagotomy without a Drainage Procedure for Duodenal Ulcer. Part I: The Effect of Highly Selective Vagotomy on Basal and Pentagastrin-stimulated Maximal Acid Output. Gastroenterology, **20**:30, 1973.
12. Kragelund, E., Amdrup, E. and Jensen, H.-E.: Qualitative and Quantitative Differences in the Response of the Stomach to Pentapeptide and Insulin Secretory Stimulation at 2–3 Month Follow-up after Parietal Cell Mass Vagotomy. Ann. Surg., **176**:656, 1972.
13. Kragelund, E., Amdrup, E. and Jensen, H.-E.: Pentapeptide and Insulin Stimulated Gastric Acid Secretion in Patients with Duodenal Ulcer before and after Selective Gastric Vagotomy and Antrum Drainage. Ann. Surg., **176**:649, 1972.
14. Madsen, P., Kronborg, O. and Feldt-Rasmussen, K.: The Gastric Emptying and Small Intestinal Transit after Highly Selective Vagotomy without Drainage and Selective Vagotomy with Pyloroplasty. Scand. J. Gastroent., **8**:541, 1973.
15. Welbourn, R. B. and Burns, G. P.: The Choice of Operation for Duodenal Ulcer on the Basis of Pre-operative Gastric Secretory Studies. With Particular Reference to the Influence of Vagotomy on Antral Function. 7. Congres International de Gastro-Enterologie, 163–177, 1964.

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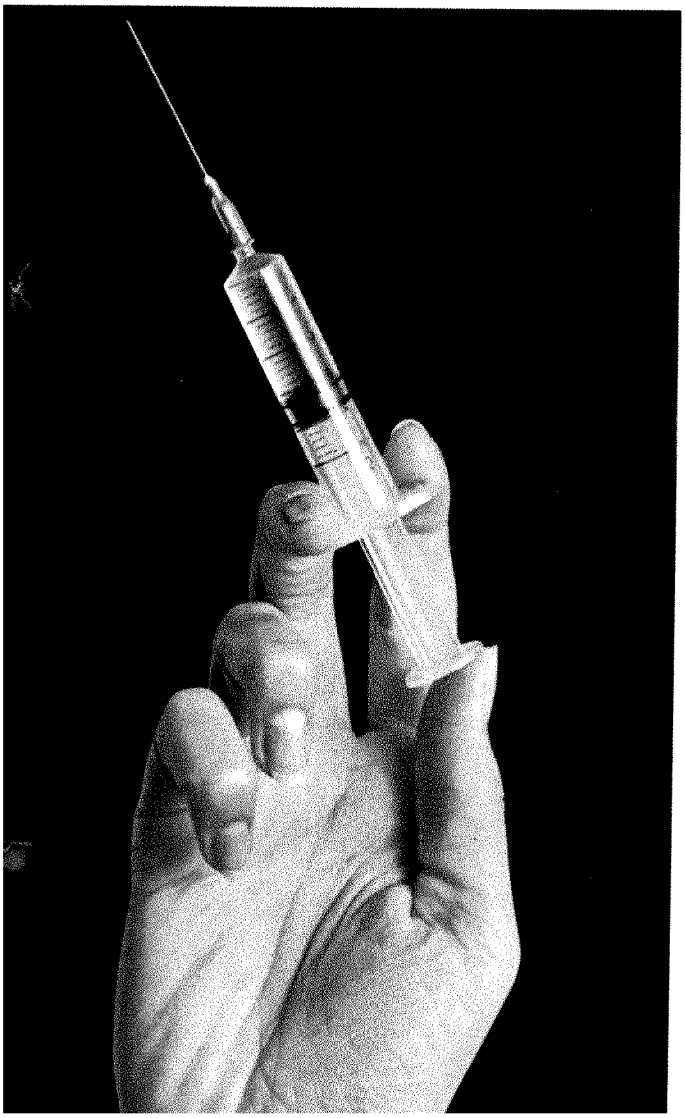

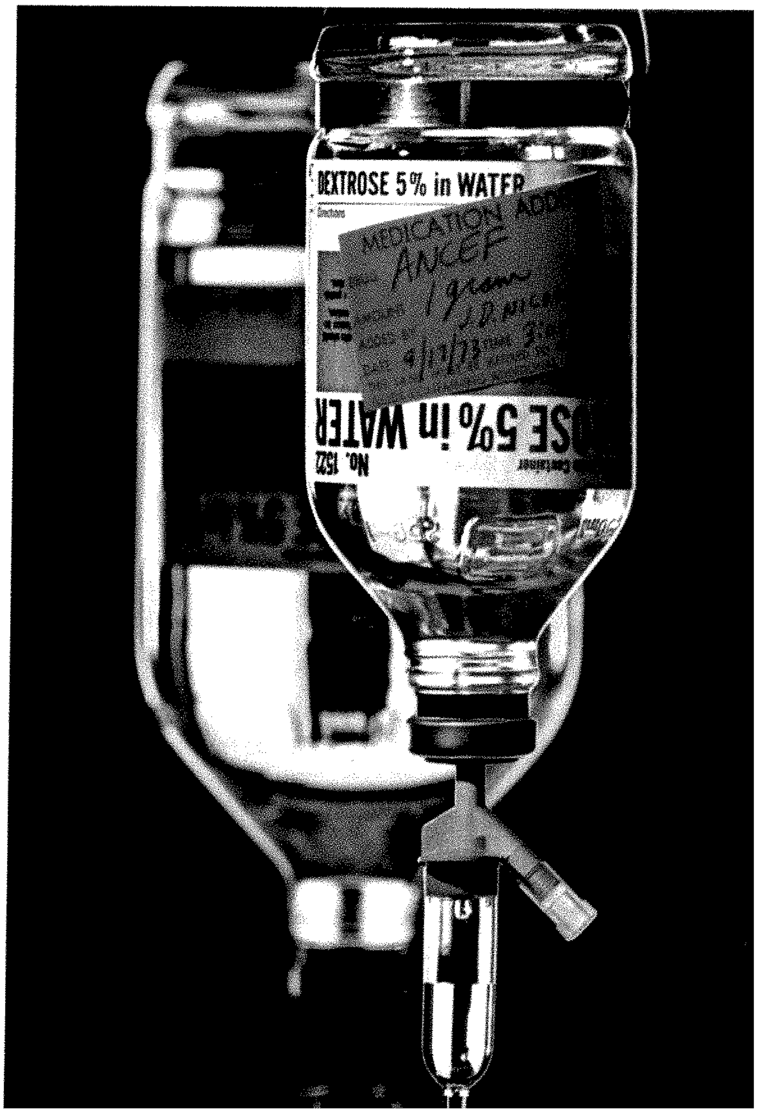

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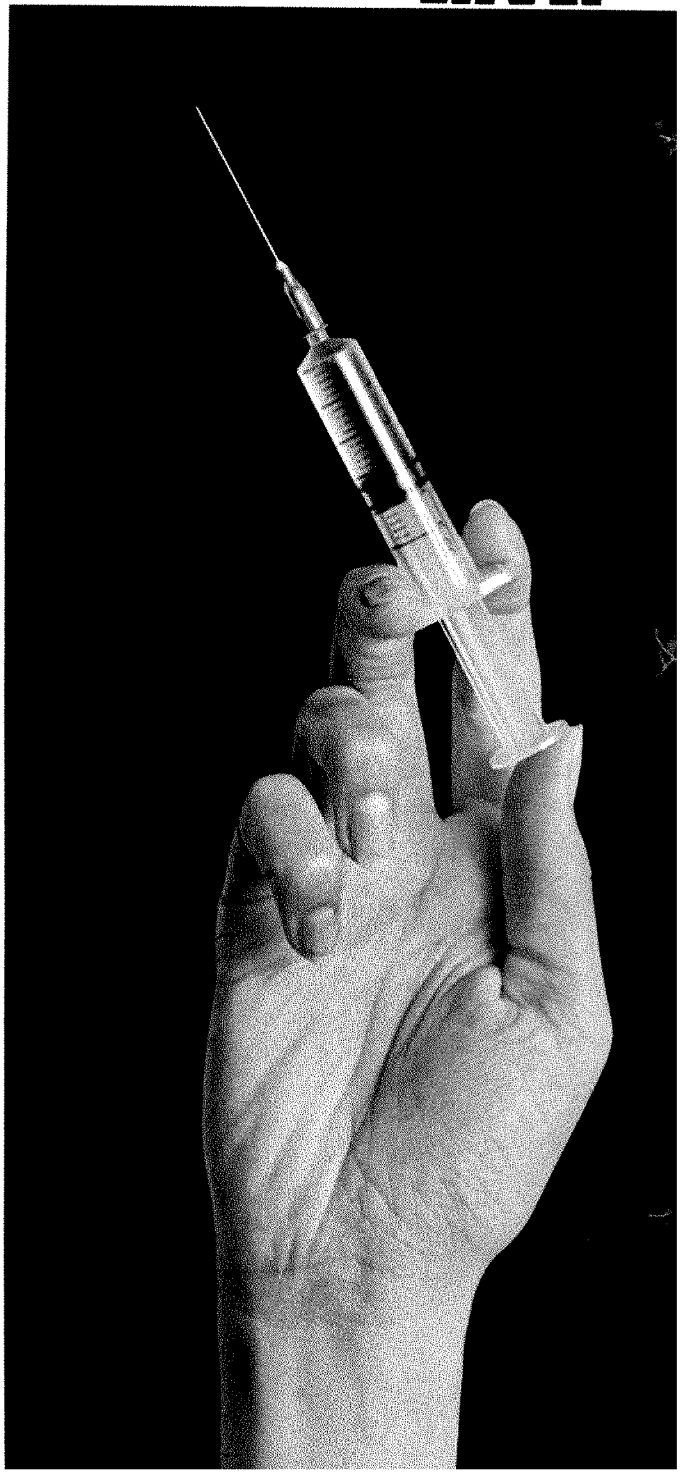

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Genitourinary tract infections due to *E. coli*, *P. mirabilis*, *Klebsiella* species and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *S. aureus*, group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus*.

Septicemia due to *D. pneumoniae*, *S. aureus*, *P. mirabilis*, *E. coli* and *Klebsiella* species.

Endocarditis due to *S. aureus* and group A beta-hemolytic streptococci.

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Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole-positive Proteus (*P. vulgaris*, *P. morgani*, *P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to 'Ancef'.

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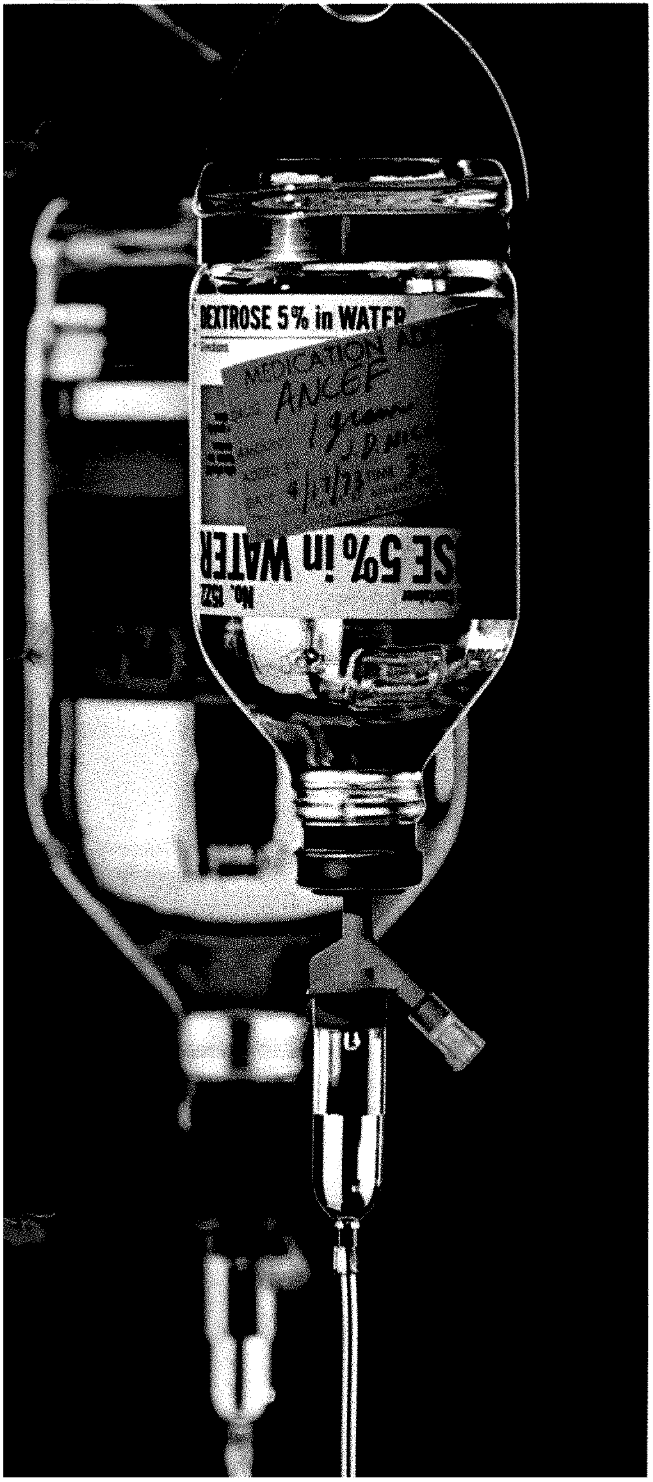

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Adverse reactions reported in the clinical trials included: pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of adverse reactions associated with 'Ancef' therapy please see brief summary of prescribing information on last page of this advertisement.

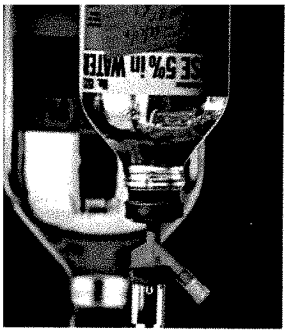
'ANCEF' Clinical Efficacy

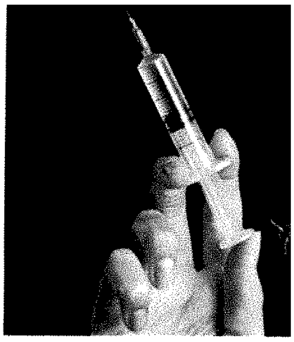
Site of Infection	Number of Patients	% "Good" or "Excellent" Response*
Respiratory Tract	377	93%
Genitourinary Tract	544	93%
Skin and Soft Tissue	122	84%
Blood and Lymph	69	81%
Bone and Joint	35	80%
Miscellaneous and Multiple Site	34	85%

The preceding results were collected from identical clinical protocols with comparable criteria of efficacy.

*Excellent: Initial improvement at 1-3 days with maximum improvement between 3-7 days. Good: Initial improvement at 2-4 days with maximum improvement between 4-10 days.

See following page for a brief summary of prescribing information including contraindications, warnings, precautions and dosage.





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ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro*:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Diplococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Diplococcus pneumoniae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli*, and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'ANCEF' IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for mild gram-positive infections is 250 mg. to 500 mg. of 'Ancef' every 8 hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every 8 hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 gram of 'Ancef' every 6 to 8 hours. 'Ancef' has been administered in dosages of six grams per day in serious infections such as endocarditis. 'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.) 60% of the normal daily dose given in divided doses q12h should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.) 25% of the normal daily dose given in divided doses q12h should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.) 10% of the normal daily dose given q24h should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dose may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

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Bladder Dysfunction and Its Manifestations Following Abdominoperineal Extirpation of the Rectum

M. KONTTURI, M.D., T. K. I. LARMI, M.D., S. TUONONEN, M.D.

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IT IS WELL KNOWN THAT BLADDER DYSFUNCTION, although sometimes transient, accompanies abdominoperineal extirpation of the rectum.[19,20] Urinary retention and the concomitant infection are the most common manifestations of morbidity (dysfunction) both in men[5,6,12] and in women.[1] Only the patients who spontaneously complain of dysuria have usually been examined. The type and severity of dysuria are assessed on the basis of the residual urine volume, radiography and/or cystometry.[5,8,17,19]

According to earlier experience in our Department of Surgery, bladder dysfunction in urologic complications may, however, be common even when the patients do not complain of it spontaneously.[10] Bladder dysfunction of milder degree may therefore pass unobserved and never be examined. For this reason, all the surviving patients, who in the last 5 years, had been operated for carcinoma of the rectum in the Department of Surgery, Oulu University Central Hospital, were included in the present study. The purpose was to study, by means of several parameters, the bladder function and urologic complications after abdominoperineal extirpation.

Material and Methods

Thirteen patients who had undergone abdominoperineal extirpation of the rectum by the Miles techniques for rectal carcinoma 6 months to 5 years, average 3 years, previously were subjected to the examination.[15] Seven were men and 6 women, age range 54–75 years, mean age 62 years. A control series of 29 patients with intact urogenital and pelvic organs underwent the same examinations. The patients were first asked whether, before or after the extirpation of the rectum, they had experienced dysuria. Irrespective of whether the reply was in the affirmative or negative, a further detailed inquiry concerning the micturition function was made by asking the questions listed in Table 1.

The following examinations were carried out to investigate bladder function and urologic delayed complications:

Examination of the urine: microscopy and urinary culture
Measurement of residual urine volume
Urinary flow study by the Kaufman uroflometer[9]
Cystometric examination[10]
Sphincterometry[13]
Urethrocystoscopy
Mictiocystography

Results

Symptoms

None of the patients had had any dysuria prior to surgery. Only 3 answered in the affirmative to the first question as to whether they had had difficulty in micturition since the extirpation of the rectum. In the detailed inquiry (Table 1), another 6 patients admitted that they had had dysuria. Only 4 had been symptom-free.

Bladder dysfunction was equally frequent among men and women. The most common symptom suggested a failure to empty the bladder. Four patients had symptoms of incontinence, and one was totally incontinent. Six patients found their symptoms considerable, 3 mild.

The present patients had been decatheterized on the 7th to 10th day after extirpation of the rectum. Seven pa-

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TABLE 1. *Distribution of the Symptoms of Bladder Dysfunction in 13 Patients 6 Months to 5 Years after Extirpation of the Rectum*

Symptoms	Men	Women	Total
Increased frequency	3	1	4
Urine flows at low pressure	1	1	2
Urine flow interruption	1	2	3
Micturition requires effort	1	2	3
Bladder fails to empty	1	1	2
Stress incontinence	1	0	1
Urine infection	1	1	2
Other symptoms	1	1	2
No symptoms	1	3	4

tients had been able to micturate immediately without any difficulty, 6 had experienced difficulties, and in 2 cases the catheter had to be re-introduced for 3–6 days. Total incontinence developed gradually in one patient after a perineal metastasis had been excised and telecobalt therapy given to this region.

Urinary tract infection was detected in the follow-up examination in the totally incontinent man who had to have an indwelling catheter, and in a woman for whom emptying the bladder was difficult and who had a residual urine of 150 ml and first-degree stress incontinence. However, 4 patients on one or more occasions, had had postoperative urinary tract infections, which had been duly treated.

Residualurine exceeding 100 ml, maximum 290 ml, was found in 5 patients. All had also symptoms of dysuria. Two had the feeling that the bladder failed to empty; in fact one of them was only able to micturate when she raised the urethra via the vagina. Two man had increased frequency of micturition, and one woman had stress incontinence.

Cystometry was interpreted as normal if the patient felt the desire to void after a fluid volume of 250–300 ml and urgency after one of 400–500 ml, by which time the intravesical pressure was 8–12 cm. On the basis of this criterion, the cystometric curve was normal for 6, hypotonic for 5 and hypertonic for 2 patients. The last 2 had urinary tract infection, and one of them an indwelling catheter. A hypotonic curve was recorded for all patients with symptoms of difficulty in emptying the bladder, and with more than 100 ml residual urine. Compared with the control series, cystometry did not show statistically significant differences for volume or pressure at the "desire to void" and "urgency" points of the means (Table 2).

TABLE 2. *The Cystometric Mean Values and their Standard Deviations at the "Desire to Void" and "Painful Urgency" Points in the Control Series and in the Present Series*

	Desire to Void		Painful Urgency	
Cystometry	Control	Present series	Control	Present series
Volume				
mean	320	310	495	435
SD	56	98.5	67	128
p		>0.05		>0.05
Pressure (cm 0.9%NaCl)				
mean	6.5	8.5	12.5	14.0
SD	1.94	6.1	3.46	8.84
p		>0.05		>0.05

TABLE 3. *Urine Flow Measured by the Kaufman Uroflometer in the Control Series and in the 12 Patients 6 Months to 5 Years after Extirpation of the Rectum*

Kaufman Uroflometer	Present series	Control series
Maximal urinary flow (ml/sec.)		
Mean	11	18
Range	8–27	2–26
SD	5, 9	8, 3
p		0, 01

Urine flow measurement revealed a maximal flow of 18 ± 8.3 ml/sec. in the control series. Of the series examined, one had an indwelling catheter, and the flow could therefore not be measured. For the remaining 12 patients, the mean maximal urine flow was 11 ± 5.9 ml/sec. and the difference from the control group was significant (Table 3). The urine flow was particularly slow in those patients who had a large residual urine volume and subjective symptoms of dysuria. In all patients with hypotonic cystometry the maximum urine flow was under 13 ml/sec., mean 7 ml/sec.

Sphincterometry of the present series showed that the sphincter tonus ranged from 16 to 30 cm physiological. Compared with the mean of the control series, 27 cm saline, the difference was not significant. However, three of the present patients with sphincter tonus above the normal mean value, had residual urines exceeding 100 ml.

Urethrocystography revealed prostatic hyperplasia in 3 male patients, and 2 of these showed symptoms of difficulty in emptying the bladder. Furthermore, 2 patients had a backward angulation of the prostatic portion of the urethra (Fig. 1). The change was attributed to an anatomical alteration following the extirpation of the rectum. Two female patients had developed a considerable cystocele since the operation, but neither had residual urine and only one had slight symptoms of dysuria.

Urethrocystoscopy disclosed changes in 6 patients, 4 women and 2 men. The trigonum in all of them seemed to have descended, forming a deep groove. The ureteral apertures were situated at the edges of the pouch, and were therefore closer to each other than normal. This, as well as the angulation of the prostatic urethra seen in urethrocystography, and also visible on endoscopy, was attributed to a dorsocaudal descent of the bladder floor since the operation.

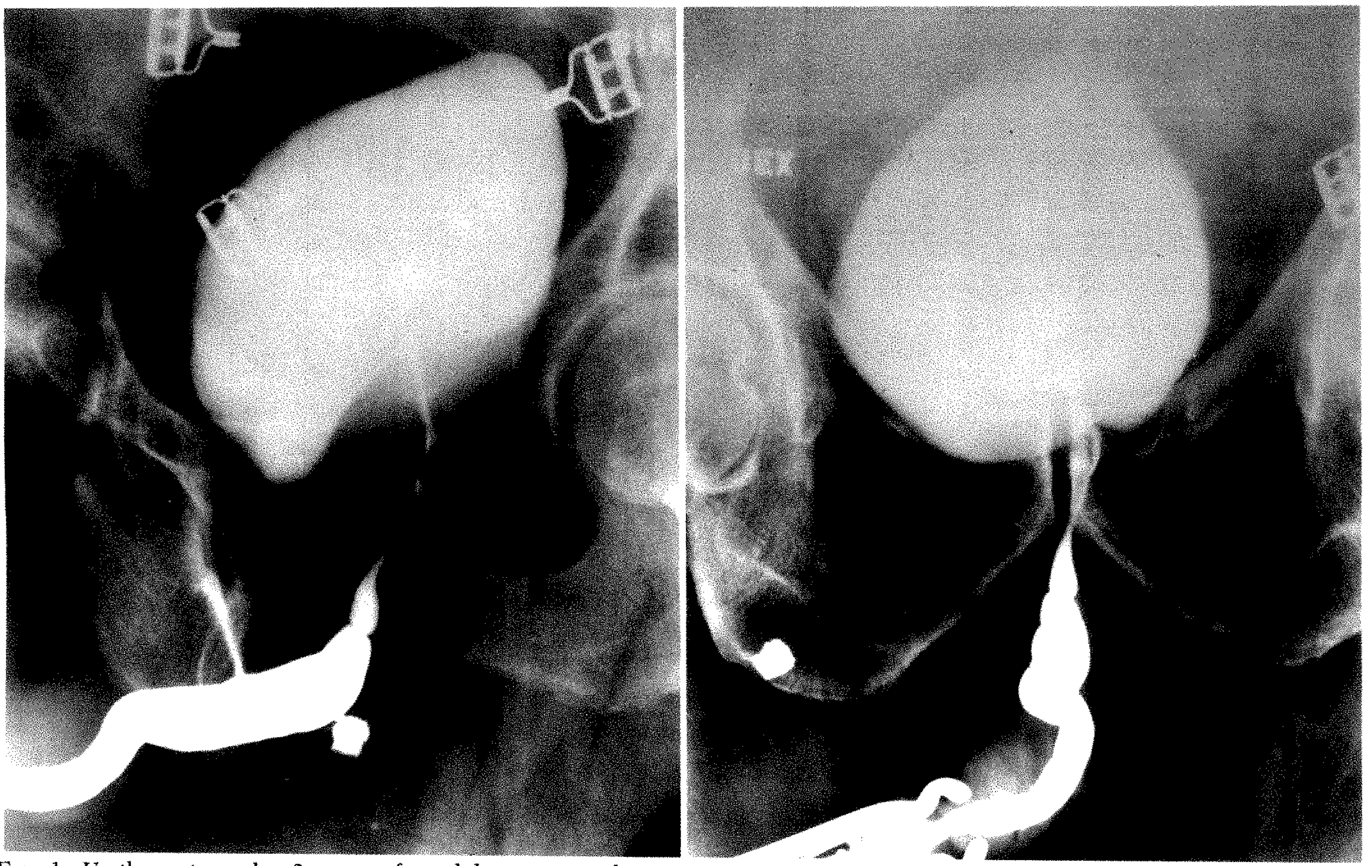

FIG. 1. Urethrocystography 2 years after abdominoperineal extirpation of the rectum shows dorsal dislocation of the bladder base (a) and angulation and left displacement of the prostrate (b). The patient had 130 ml of residual urine and the maximum urine flow was 8 ml/sec.

Discussion

The results gave new information about bladder dysfunction and its manifestations following abdominoperineal extirpation of the rectum. In agreement with earlier authors[5,19,20] it was found that impaired emptying of the bladder, urinary retention and urologic infections were the most frequent late complications after extirpation of the rectum. But in the present series the incidence of these symptoms was much higher than has been reported earlier.[7,19] The difference is apparently due to the fact that all the patients living 6 months to 5 years after the extirpation of the rectum were subjected to these examinations. It appeared that, as has been observed previously in our Department of Surgery,[10] 6 of 13 patients did not admit to having dysuria until the follow-up examinations were in progress. It was also found that even in the case of mild symptoms, some form of the bladder function tests and examinations disclosed their existence.

The incidence of urinary tract infection at the moment of the follow-up was the same as reported by other authors,[1,18] but detailed medical history revealed that another 4 had had an earlier, curatively treated urinary tract infection.

Cystometry after extirpation of the rectum can be either hypotonic, normal or hypertonic. It was hypertonic in 2 of the present patients, both of whom already had an injection in progress and one additionally a contracted bladder following irradiation, and an indwelling catheter. Hypotonia is common after extirpation of the rectum and produces symptoms arising from bladder neck obstruction by prostatic hyperplasia or some other factor.[2] However, the cystometry of 6 of the present patients was normal, although three of them had residual urines exceeding 100 ml and retarded urine flow. Cystometry is useful mainly for the diagnosis of denervated bladder,[10] but alone, without further examinations, it does not provide a complete picture of bladder dysfunction.[16]

In the urinary flow study, an examination we have not found reported in the literature after extirpation of the rectum, the emptying rate of the bladder was found to be distinctly retarded. Maximal urinary flow was slow in all with a residual urine volume exceeding 100 ml.

Bladder dysfunction after extirpation of the rectum may develop for various reasons. One reason is bladder neck obstruction or prostatic hyperplasia[2,21] and this has led to a recommendation that prostatectomy should be combined with extirpation of the rectum.[4] Prostatic hyperplasia was the main reason in two of the present patients.

Some authors consider that the surgical interruption of pelvic nerves[14] and extensive dissection immediately adjacent to the lower urinary tract[3] are associated with at least a temporary inability to void in most patients recovering from abdominoperineal resection. However, none of the present patients showed complete denervation of the bladder, which would have been visible in cystometry. According to McCrea and Kimmel,[14] the pelvic nerves run in 2 bundles along each side. In extirpation of the rectum, a medial bundle is often traumatized, but a lateral one only if dissection extends to the lateral wall of the true pelvis. This may also help to explain why bladder dysfunction is less common in amputation of the rectum for ulcerative colitis, in which dissection is performed close to the intestine, than in amputations for carcinoma.[19]

The anatomical change in the position of the bladder following extirpation of the rectum is one of the causes of dysuria. As a result of the operation, the bladder loses the support of its posterior wall and descends posteroinferiorly especially in women.[11] In 6 of the present patients, according to urethroscopy, the trigonum in particular was indented and urethrocystography, additionally, revealed a backward angulation of the prostatic portion of the urethra in 2 men. Two female patients had developed cystocele.

Earlier studies of bladder dysfunction following extirpation of the rectum have devoted no attention to the disturbed function of the muscles of the pelvic floor. According to Muellner,[16] however, coordinated movement of the pelvic floor muscles is essential for micturition. In the initial phase of micturition, these muscles are relaxed, permitting the bladder to descend at the same time as the bladder neck opens. Thus, if it is necessary to traumatize pelvic floor muscles in connection with the extirpation of the rectum and the patient is still in pain, micturition fails immediately after the operation. It is probable that in a number of patients the coordinated function of pelvic floor muscles is never again restored, not even later. This view is supported by Couvelaire's[5] observation of a patient who developed a complete urinary retention after a painful metastasis had appeared on the floor of the pelvis, although it presented no mechanical hindrance to urinary flow. One of the present patients, after excision of a perineal metastasis, developed incontinence which, of course, may also arise when extensive perineal dissection injures the pudendal nerve.[20] The low incidence of bladder dysfunction following extirpation of the rectum for ulcerative colitis may also be partly explained by the more sparing dissection with which there is less interference with the pelvic floor muscles.

Summary

A careful analysis of the symptoms in 13 patients subjected to abdominoperineal extirpation of the rectum showed that 9 of these patients suffered from dysfunction of the bladder. Even the mild cases showed a residual urine volume exceeding 100 ml, or else a retarded urinary flow. Cystometry, sphincterometry, urethrocystography and urethrocystoscopy supplemented the overall view of the dysfunction. Causes of postoperative dysfunction are suggested to comprise bladder neck obstruction or prostatic hyperplasia, postoperative anatomical changes of the bladder, partial denervation, and a poor neuromuscular coordination ability of the pelvic floor muscles.

References

1. Apakova, S. A.: Urologic Complications after Surgery for Rectal Cancer. Khirur., **45**:114, 1969.
2. Baumrucker, G. O. and Shaw, J. W.: Urologic Complications Following Abdominoperineal Resection of the Rectum. Arch. Surg., **67**:502, 1953.
3. Campell, M. F.: Urologic Complications of Anorectal and Colon Surgery. Am. J. Proctol., **12**:43, 1961.
4. Cook, E. N., Tencote, H. W. and Potter, W. M.: Urinary Retention Following Operations on the Bowel. J. Urol., **89**:255, 1963.
5. Couvelaire, R.: Urination Disorders in Patients with Rectal Amputation. Ann. Chir., **19**:1682, 1965.
6. Cukier, J.: The Urethrovesical Complications of the Surgery of Extended Exeresis of Cancer of Rectum. Cah. Med., **11**:57, 1970.
7. Gallizia, G.: Urinary and Genital Complications after Radical Surgical Intervention for Rectosigmoid Carcinoma. J. Urol. Néphrol., **75**:711, 1969.
8. Glass, R. L.: Urinary Retention after Abdominoperineal Resection of the Rectum in Male Patients. Mo. Med., **63**:990, 1966.
9. Kaufmann, J.: A New Recording Uroflometer. J. Urol., **78**:97, 1957.
10. Kontturi, M.: Investigations into Bladder Dysfunction in Prolapse of Lumbar Intervertebral Disc. Ann. Chir. Gynaecol. Fenn., **57**:suppl. 162, 1968.
11. Kusmierski, S., Krakowski, J., Moskal, M., Kubicki, B. and Lukasiewicz, S.: Examination of Urinary Tracts in Patients Having Had to Undergo the Abdominoperineal Amputation of the Rectum for its Carcinoma. Pol. Przegl. Chir., **43**:1007, 1971.
12. Leadbetter, G. W. and Leadbetter, W. F.: A New Approach to the Problem of Urinary Retention Following Abdominoperineal Resection for Carcinoma of the Rectum. Surg. Gynecol. Obstet., **107**:333, 1958.
13. Leander, H. G.: Disturbances in Evacuation Mechanism of the Bladder. Nord. Med., **22**:1179, 1942.
14. McCrea, L. E. and Kimmel, D. L.: New Concept of Vesical Innervation. Relationship of Vesical Innervation to Bladder Management Following Abdominoperineal Proctosigmoidectomy. Am. Arch. Surg., **66**:84, 1953.
15. Muellner, S. R.: The Physiology of Micturition. J. Urol., **65**:805, 1951.
16. Rossi, R., Acerbi, A. and Coppi, F.: Urination Disorders Caused by Amputation of the Rectum by Abdominoperineal Approach. Arch. Ital. Urol. Nephrol., **42**:430, 1969.
17. Sankey, N. E. and Heller, E.: The Urologic Complications of Abdominoperineal Resection. J. Urol., **97**:367, 1967.
18. Thorsøe, H.: Urological Complications of Abdominoperineal Extirpation of the Rectum. Ugeskr. Laeger, **133**:739, 1971.
19. Ward, J. N. and Nay, H. R.: Immediate and Delayed Urologic Complications associated with Abdominoperineal Resection. Am. J. Surg., **123**:642, 1972.
20. Wemeau, L. and Mazeman, E.: Urinary Disorders in Patients with Rectal Amputation. Ann. Chir., **19**:1680, 1965.

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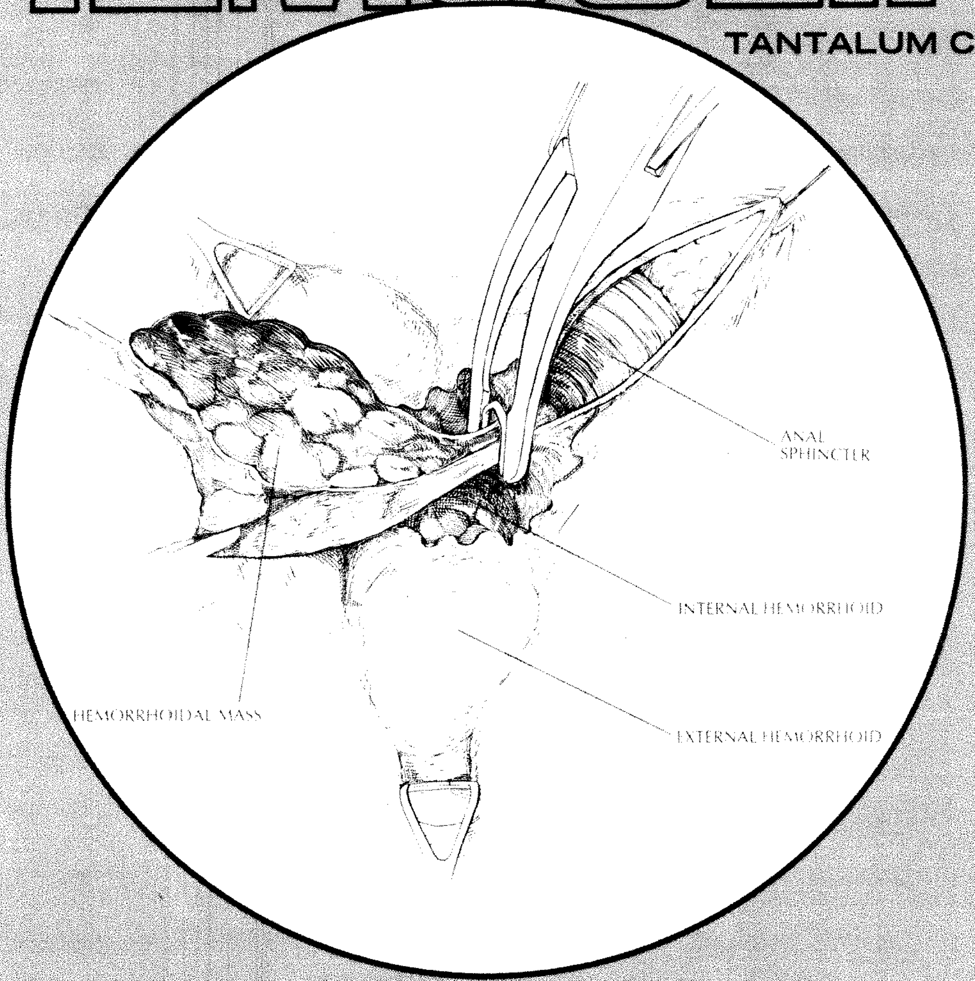

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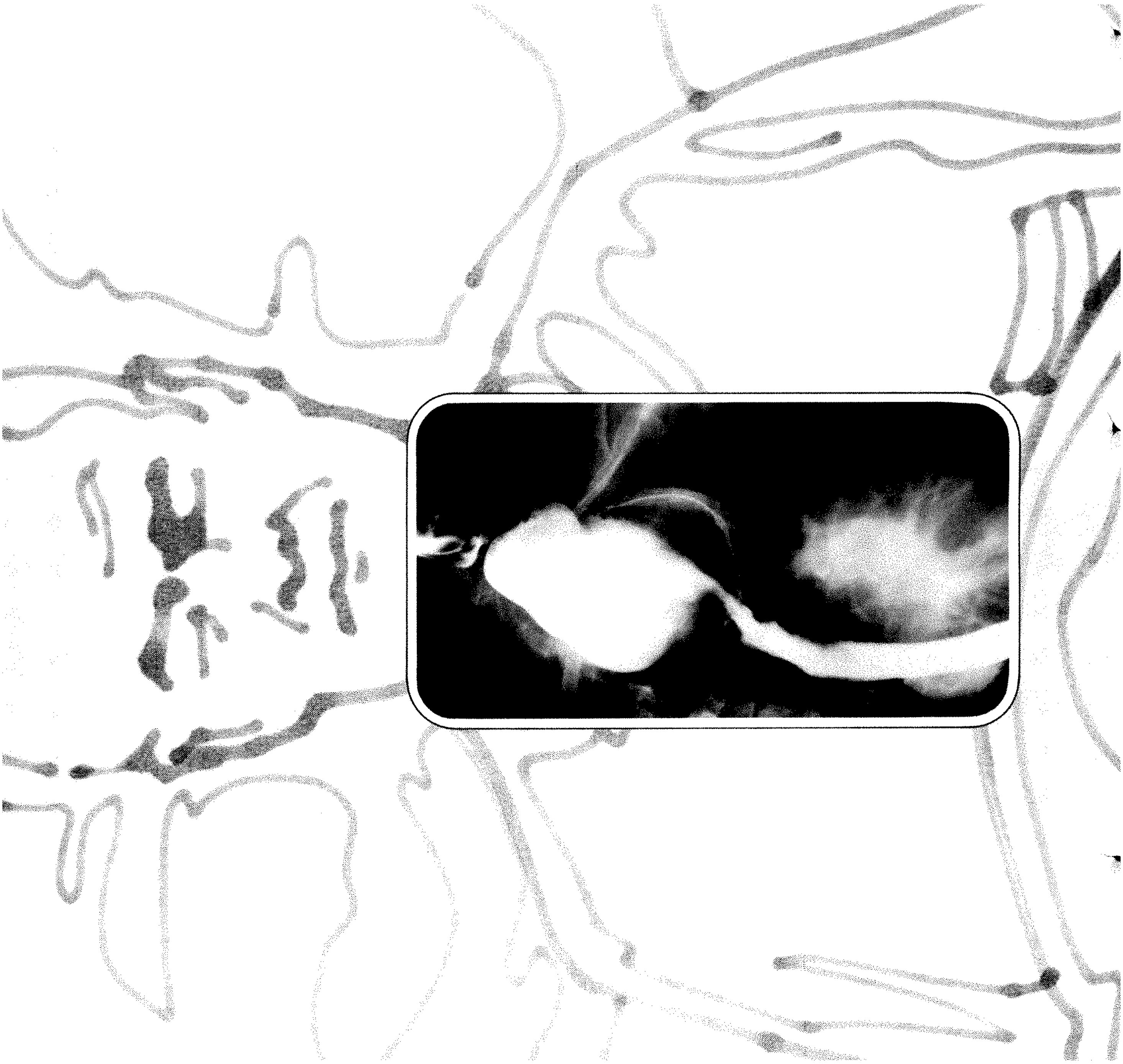
Surgical nutrition—a case history: giant esophageal diverticulum; surgical treatment followed by esophagocutaneous fistula

Management of medical-surgical problems frequently requires a multifaceted approach—each facet contributing to the patient's outcome. The following case history demonstrates the allied roles of surgical management and sound nutritional support.

The patient: A 72-year-old man with a history of severe dysphagia was admitted to the hospital because his complaint had become markedly worse in the past few months. He could hardly swallow and regurgitated a considerable portion of what he did manage to eat. Thin almost to the point of emaciation, he was 68 inches tall and weighed 126 pounds. The patient was well below his desirable weight.

X-ray studies showed a massive cricopharyngeal diverticulum, extending down to the level of the aortic arch. No other abnormal conditions were found.

Surgical treatment: At operation the opening at the back of the esophagus was found to be about 2 inches in diameter. Extremely dense adhesions surrounded the diverticulum, and resection was accomplished only with



considerable difficulty. The excised tissue showed evidence of chronic inflammation, but no tumor was seen. A Levin tube was threaded through the esophagus under direct vision, and a Penrose drain was placed in the incision. The patient withstood the procedure very well.

Postsurgical course: For 3 days following the surgery, the wound seemed to heal normally; the patient was swallowing well, and his condition improved daily. However, when the Penrose drain was removed, an inflamed fistulous tract was discovered in the wound. An antibiotic and streptokinase-streptodornase were administered. Drainage from this opening continued for about 10 days.

Nutritional management: Inability to eat had caused deterioration of the patient's nutritional status as evidenced by gross weight loss. To provide for an optimal nutritional condition to meet increased postsurgical metabolic needs, Vivonex High Nitrogen was used and clear liquids were given as desired. Postoperatively, the patient experienced no weight loss. His nutritional status was greatly improved.

Outcome: Surgical results were good as demonstrated through regained normal function of the esophagus. With the aid of drug therapy, the postsurgical fistula closed spontaneously. When discharged the patient was in excellent condition, nutritionally stable, able to take a full diet and rapidly regaining weight.

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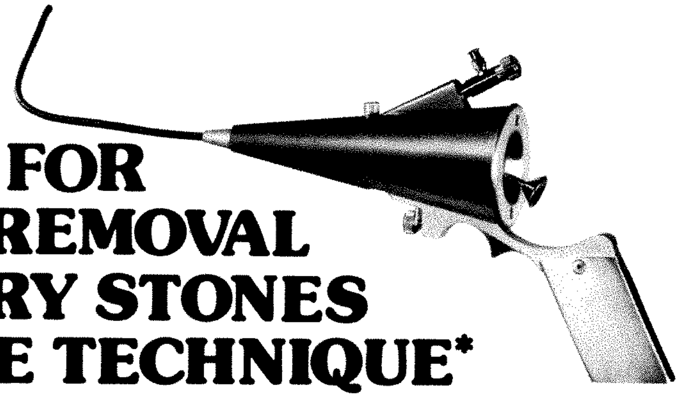

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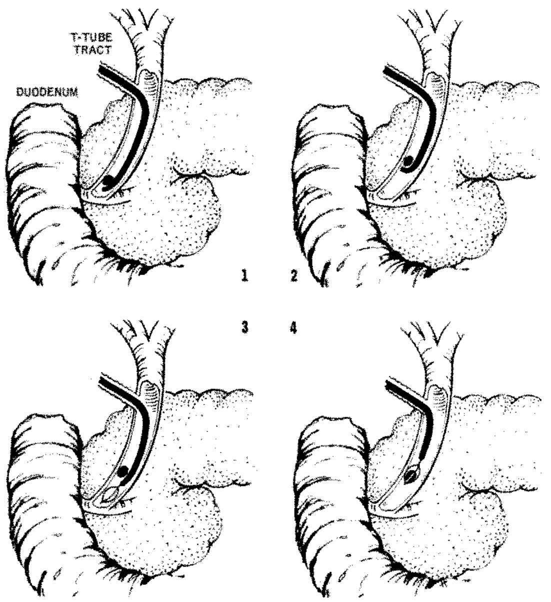

*REFERENCE

Burhenne, H. J., Non-operative Retained Biliary Tract Stone Extraction — A New Roentgenologic Technique, AMER. J. ROENTGENOLOGY, Vol. CXVII, No. 2, pp. 388-399, February 1973.

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Neomycin Toxicity from Porcine Skin Xenografts

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UNDERHILL[6] first showed with vital dyes that the burn surface is absorptive. Almost any substance applied to burned skin can be absorbed, and may cause systemic toxicity when the balance of dose and susceptibility favor it. Toxicity has been reported for the topical agents now in use and for many that have been abandoned. When porcine skin xenografts were introduced, freedom from conventional pharmacologic toxicity was expected to be one of their advantages. Although immunologic problems were anticipated, they have not been a significant problem in skin graft dressings which cross species lines. Pigskin itself does appear, so far, to be harmless; but added substances may not. We have observed renal and otic toxicity due to neomycin in porcine skin xenografts procured through a commercial supplier.

Materials and Methods

Porcine Skin Xenograft

Pigskin was supplied in rolls measuring 3 inches by 4 feet (1 square foot); thickness varied from 0.2 to 0.4 mm. The package label stated that neomycin was used in its preparation.

Neomycin Assay

Neomycin in blood and urine was determined by microbiological agar diffusion.[4] Neomycin in pigskin was assayed by 2 methods. Results from both were similar.

1. One inch squares of neomycin were submerged in 2 ml of pH 8 Sorenson's phosphate buffer, incubated at 4°C for 1–4 days, then assayed as for blood.
2. Circular pieces 6 mm in diameter were applied directly to antibiotic assay plates, inhibition zones were measured and compared to disc standards.

Chromatography of Antibiotics

Urine and appropriate standards were run on paper in the chloroform-methanol-ammonia system described by Wagman *et al.*[7] Chromatograms were dried and developed by application of the developed paper to large plates of Difco antibiotic assay medium #5 seeded with *Bacillus subtilis* AT66-6633. After 20 minutes, the paper chromatogram was removed and the plate incubated overnight at 37°C. With this technique, visible zones of growth inhibition (the autobiogram) are induced by diffusion of the separated antibiotic into the agar.

Results

Neomycin content of the porcine skin ranged from 85 to 250 mg per square foot, or from 0.5 to 1.5 grams of neomycin for each application of 6 square feet to the patient described in Case 1 below. The lower values were found in the thinner samples, and the higher in the thicker pieces.

Case Reports

Case 1. A 72-year-old female fell into a bathtub filled with hot water. Her back and arms were burned; the depth was estimated to be deep partial thickness, totaling 35% of body surface. Fluid therapy was conventional and uncomplicated. She was given

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penicillin (10^6 units per day) for 5 days as prophylaxis against Streptococcal infection. No other parenteral antibiotics were used. A small area on one ankle of less than 1% body surface was treated with a topical mixture of neomycin, polymyxin and bacitracin for the first 6 postburn days. From the time of admission the burn surface was covered with porcine xenographs held in place by elastic mesh; they were changed every 3 days. Each dressing change required 6 square feet of xenograft. The patient had no history of preexisting renal disease. Her blood urea nitrogen was 25 mgm/100 ml on admission, and fell to 7 mgm/100 ml after acute phase therapy. On the 22nd postburn day it was 42; when measured again on the 29th day it was 82. Xenografting was discontinued on the 29th postburn day when renal insufficiency had become obvious and deafness was observed. On the 32nd postburn day, 3 days after the use of porcine skin had been stopped, the blood neomycin level was 4.5 micrograms/ml. The blood urea nitrogen was normal 3 weeks later, but hearing loss continued, and audiometry showed a profound neurosensory hearing deficit. The burn itself went on to heal without grafting but the patient remains totally deaf and communicates only by writing and lip reading.

Case 2. A 61-year-old man with normal renal function (serum creatinine 1.1 mgm/100 ml) was admitted for bilateral ankle ulcers due to arteriosclerotic peripheral vascular disease. Initially covered by a leathery eschar, the ulcer beds were converted to a clean granulating surface by repeated dressings and debridement. One square foot of porcine skin xenograft was then applied as a biologic dressing. Neomycin level was measured in 6 blood samples obtained 1½ to 24 hours after application of the graft. The maximum neomycin concentration in the blood was 6.7 mcg/ml after 6 hours (Fig. 1). Total urinary excretion of neomycin in the 48 hours after application was 24 mgm. The antibiotic activity in urine was identified as neomycin by chromatography; the urine also contained a small amount of gentamicin, probably due to gentamicin ointment applied when the porcine skin grafts were removed (Fig. 2).

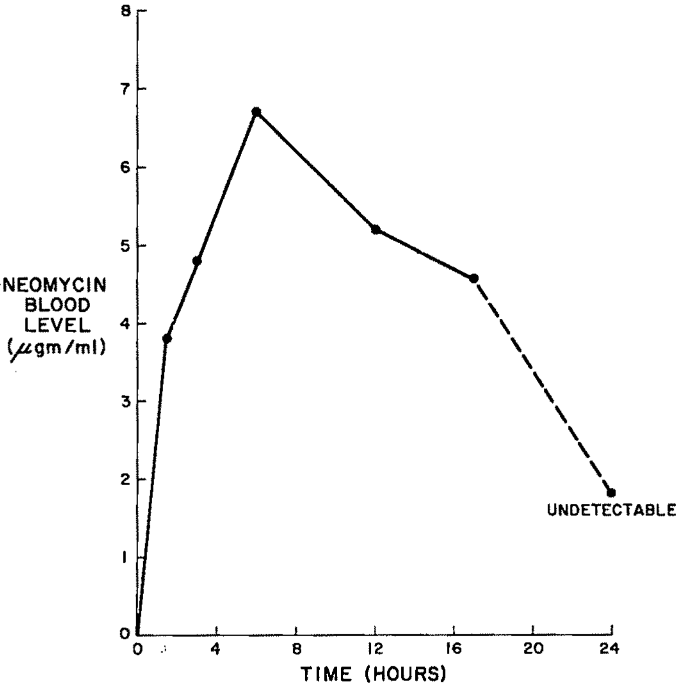

FIG. 1. Concentration of neomycin in blood after application of 1 square foot of neomycin treated porcine xenograft.

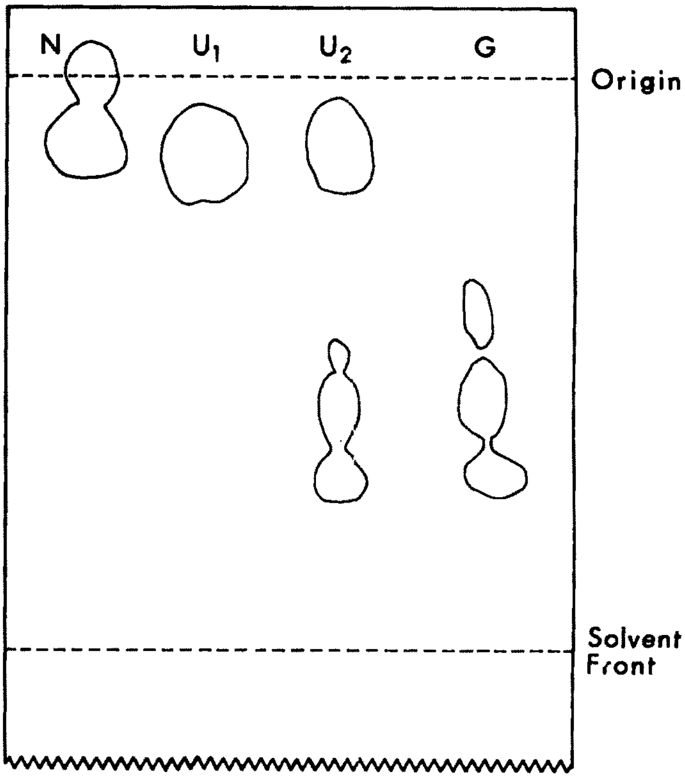

FIG. 2. Autobiogram showing reference neomycin (N) and gentamycin (G), as well as antibiotic material in urine from patient in case 2 on first (U_1) and second (U_2) day after pigskin graft had been applied. Note U_1 contains only neomycin whereas U_2 contains neomycin and gentamycin's three components: C_1^a, C_2, and C_1 (furthest from origin). Only one neomycin component, presumably neomycin B, appeared in the urine, but the reference powder contained two active components.

Discussion

The evidence favors neomycin as the probable cause of ototoxicity and nephrotoxicity in the patient of Case 1; the symptoms were characteristic, and this drug can cause systemic toxicity after topical application. Trimble[5] comments that each time a different preparation of neomycin becomes available reports of ototoxicity after use of the drug by the new route appears. The single neomycin blood level that was measured in the first patient (4.5 micrograms/ml) may or may not be toxic in itself, however, the presence of neomycin at this concentration 3 days after the use of pigskin was discontinued implies that the peak level had been much higher. A single number cannot be assigned as the threshhold for neomycin toxicity, for both time and dose are important; prolonged exposure with even minimal absorption can be toxic.[1] a sustained level of greater than 3 micrograms/ml at 24 hours may represent a toxic concentration.[3]

In Case 1, the total dose applied to the burn surface was extremely large, between 0.5 to 1.5 gms. This dose, applied every 3 days for 29 days, totals 4.5 to 13.5 gms.

Combining the data above with information available from the literature, makes possible an approximation of neomycin absorption from one square foot of porcine skin, i.e.:

1) The total urine excretion for 48 hours was 24 mgm.

2) 30–50% of parenteral neomycin is excreted.[2]

3) Therefore, 48 to 80 mgm was absorbed from one square foot of porcine skin.

4) Since assays showed from 43 to 249 mgm of neomycin per square foot of fresh graft absorption could range between 19 to 96% of the total amount of neomycin applied with porcine skin to the burn surface.

While it is recognized that the absorption from a wound may vary, at least for sulfamylon a partial thickness burn is the most efficient absorbing surface;[8] the total systemic dose would lie between 4.5 and 13.5 grams.

Since the above observations were made the manufacturer has changed preparation procedures to lower neomycin content to 4% of original levels. However, xenografts are available from several sources, and it is plainly important for the supplier to monitor antibiotic content of the prepared material and for the user to follow antibiotic levels in the patients treated with it. Another question is raised that is not answered by these data: whether or not the clinical effect of porcine xenografting is due in part to topical antibiotics.

Summary

Renal failure and deafness followed the use of commercial porcine xenografts in a burned patient. Neomycin blood level was elevated (4.5 micrograms/ml) when first measured, three days after removal of the grafts. The xenografts which had been used were found to contain substantial amounts of neomycin. Observations in a second patient showed absorption of neomycin from the xenograft, as demonstrated by urinary recovery of antibiotic. The observed toxicity is attributed to neomycin absorption through the burn surface, and measurement of antibiotic blood levels is advised when grafts contain potentially toxic antibiotics.

Acknowledgments

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References

1. Berk, D. P. and Chalmers, T.: Deafness Complicating Antibiotic Therapy of Hepatic Encephalopathy. *Ann. Intern. Med.*, 73:393, 1970.
2. Bogen, E. quoted by Jawetz, E.: Polymyxin, Neomycin, Bacitracin. New York, Medical Encyclopedia Inc., 42, 1956.
3. Line, D. H., Poole, G. W. and Waterworth, P.M.: Serum Streptomycin Levels and Dizziness. Tubercle, 51:76, 1970.
4. Sabath, L. D., Casey, J. L., Ruch, A., Stumpf, L. L. and Finland, M.: Rapid Microassay of Gentamicin, Panamycin, Neomycin, Streptomycin and Vancomycin in Serum or Plasma. J. Lab. Clin. Med., 78:457, 1971.
5. Trimble, G. X.: Neomycin Ototoxicity: Dossier and Doses. New. Engl. J. Med., 281:219, 1969.
6. Underhill, F. P., Kapsinow, R. and Fisk, M. E.: Studies on the Mechanism of Water Exchange in the Animal Organisms. I. The Nature and Effects of Superficial Burns. Am. J. Physiol., 95:302, 1930.
7. Wagman, G. H., Marquez, A. J. and Weinstein, M. J.: Chromatographic Separation of the Components of the Gentamicin Complex. J. Chromatog., 34:210, 1968.
8. White, M. G. and Asch, M. J.: Acid Base Effects of Topical Mafenide Acetate in the Burned Patient. New Engl. J. Med. 284:1281, 1971.

Neonatal Adrenal Pseudocyst Mimicking Metastatic Disease

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WE HAVE RECENTLY TREATED AN INFANT with a benign adrenal pseudocyst which presented as a chest wall mass, showed roentgenographic evidence of rib destruction, suggesting metastatic disease, and was managed successfully by surgical drainage, with subsequent resolution of the mass and reossification of the rib. This unusual presentation of a benign adrenal pseudocyst has not been previously described. Although the findings of a suprarenal mass with peripheral curvilinear calcification and downward displacement of the adjacent kidney are highly suggestive of an adrenal cyst, this diagnosis is infrequently made preoperatively. Of the approximately 250 cases of adrenal cysts reported in the literature, fewer than 5% occurred in children, with only 9 cases being reported in neonates.[9]

Case Report

AGS #545279. A 2-month-old Mexican-American male was admitted on 9/20/72, 2 days after his mother noted a hard, subcutaneous mass over his right chest wall. Although not examined by a physician, the mother denied any postnatal irritability, jaundice, weight loss, fever, or gastrointestinal symptoms in the infant. He weighed 7 lbs. 8 oz. at birth and was the product of a fullterm delivery. He was the third Rh positive child born to his Rh negative mother, who experienced mild hypertension during the third trimester and a one-day leak of amniotic fluid during the eighth month of her pregnancy.

Physical Examination. The patient was a well-developed, alert infant in no distress. Vital signs were normal, he was afebrile, and weighed 10 lbs. 12 oz. There was a 3 × 5 cm. hard, non-movable mass in the right lower postero-lateral chest wall over the region of the tenth rib, without surrounding warmth, erythema, or tenderness. Breath sounds were normal. The liver edge was palpable at the right costal margin and the spleen tip was also palpable. The sensation of fullness was noted in the right flank in the region of the upper pole of the kidney. There was no significant adenopathy. The remainder of the examination was unremarkable.

Laboratory Data. Hgb 9.6 grams, Hct 30%, Wbc 11,900, S 31, B 6, L 58, M 3, E 2, BUN 7 mg%, Creatinine 0.4 mg%, Potassium 5.4 meq/L, Sodium 136 meq/L, Chloride 104 meq/L, Bicarbonate 20 meq/L, FBS 93 mg%, SGOT 29 U, SGPT 29 IU, LDH 155 IU, Alkaline Phosphatase 15.6 U, PT 11.2/11.8, PTT 27.9/28.9, Urinalysis, urinary VMA and Catecholamines, Tuberculin and fungal skin tests, bone marrow, and CSF examinations were normal.

X-Ray Studies. Chest X-ray demonstrated a soft tissue mass in the right lateral chest wall with destruction of the lateral aspect of the right tenth rib. A rim-like calcification measuring 6 cm. in diameter was noted in the right upper quadrant. An IVP (Fig. 1) showed the cyst-like lesion displacing the upper pole of the right kidney downward and postero-laterally. The collecting systems and bladder were otherwise normal. Liver-spleen scan showed an extrinsic defect in the right lobe of the liver. A metastatic skeletal series was normal. An abdominal echogram revealed a cystic mass in or above the upper pole of the right kidney.

Hospital Course. On 9/25/72, the patient was taken to the operating room with a tentative diagnosis of metastatic disease from the suprarenal mass to the rib and chest wall. The chest wall lesion was found to be a thick walled extrapleural pseudocyst pressing against and eroding the tenth rib. A frozen section biopsy of the cyst wall revealed inflammatory tissue. On attempting to obtain a deeper biopsy, the cavity of the pseudocyst was entered, with the expression of 30 ml. of creamy, non-odorous fluid. An operative sinogram (Fig. 2) revealed that the chest wall mass was an upward extension of the calcified adrenal pseudocyst. After several biopsies of the cyst had been obtained, the cavity was drained with a rubber catheter, and the procedure was terminated. Gram stains, cultures for bacteria, AFB, and fungi were all negative. Biopsy specimens revealed only inflammatory

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tissue. Postoperatively, the patient remained afebrile, and over a 2-week period the cavity closed and both the suprarenal and chest wall masses diminished greatly in size (Figs. 3 and 4). Reossification of the destroyed rib was noted within two weeks of surgery. Subsequent follow-up X-rays 10 weeks postoperatively have shown continued remodelling of the tenth rib and shrinkage of the calcified mass. The infant has gained 2 pounds and is clinically well.

Discussion

The first benign cyst of the adrenal gland was described by Greiselius in 1670.[5] Most authors classify adrenal cysts into 5 categories: 1) parasitic cysts; 2) retention cysts (congenital glandular); 3) cystic adenoma; 4) endothelial (lymphogenic or vascular degenerative cysts); and 5) pseudocysts. (3) The last type accounts for nearly 50% of adrenal cysts.[1]

Pseudocysts originate from hematomata in or around the adrenal gland, or, rarely, from a hematoma within a neoplasm. Organization of the hemorrhagic area results in a large, usually unilocular cyst, the walls of which are composed of dense fibrous tissue and not lined with epithelium. Rim-like calcification of the mass with evidence of downward displacement of the adjacent kidney seen on intravenous urography are virtually pathognomonic of an adrenal cysts. However, extension into the thoracic region and erosion of a rib by such a benign process has not been previously described.

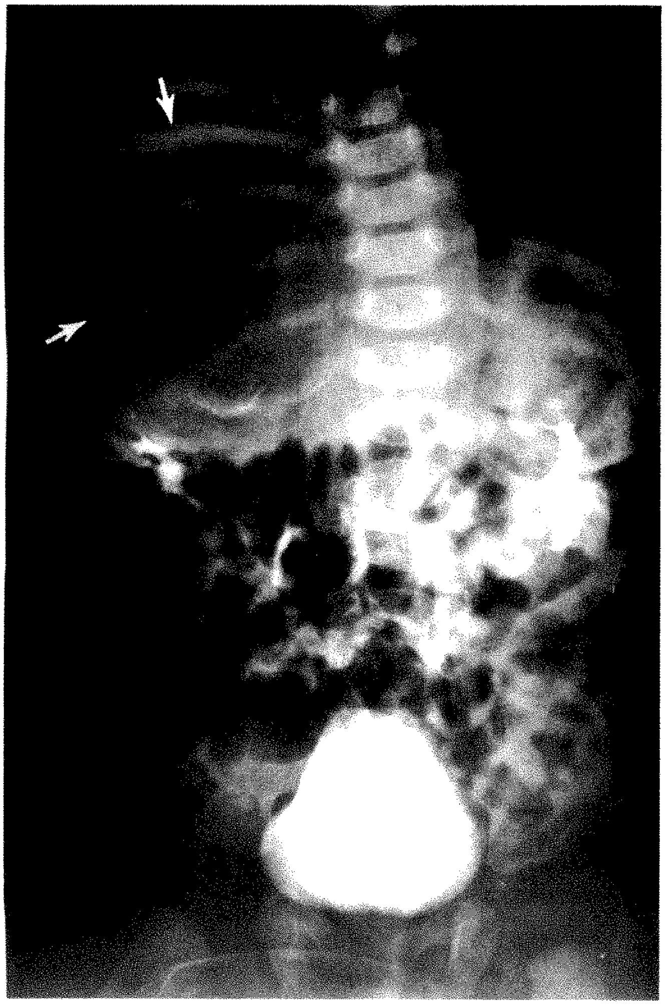

FIG. 1. Downward displacement of the right kidney by the cystic mass and destruction of the right tenth rib.

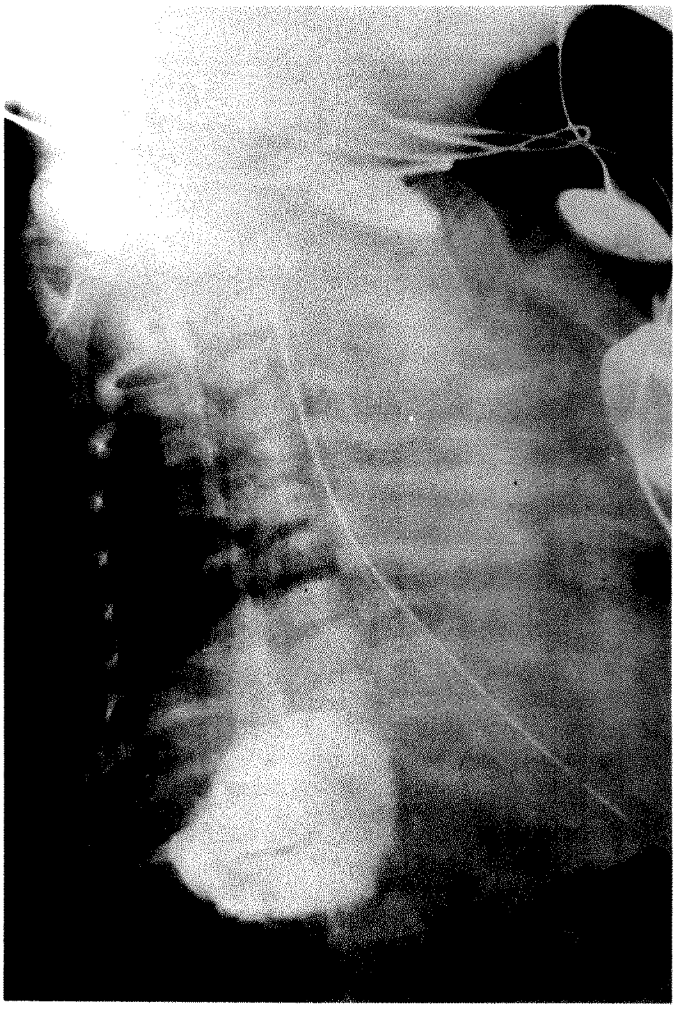

FIG. 2. Operative sinogram revealing continuity between chest wall and suprarenal masses.

Adrenal cysts in infants are usually of the pseudocyst variety,[9] and are felt to be secondary to neonatal adrenal hemorrhage. Such hemorrhage is a well recognized entity, being reported in up to 1% of neonatal autopsies.[6] Trauma associated with delivery is recognized as the single most important etiology factor, although infection, hemorrhagic disease of the newborn, burns, hemophilia, syphilis, leukemia, incompatible blood transfusions, and adrenal vein thrombosis have been rarely implicated.[3]

The adrenal gland is nearly ⅓ the size of the kidney at birth, making it more susceptible to trauma at the time of delivery. Although neonatal hemorrhage may be bilateral, right sided involvement is more common, pos-

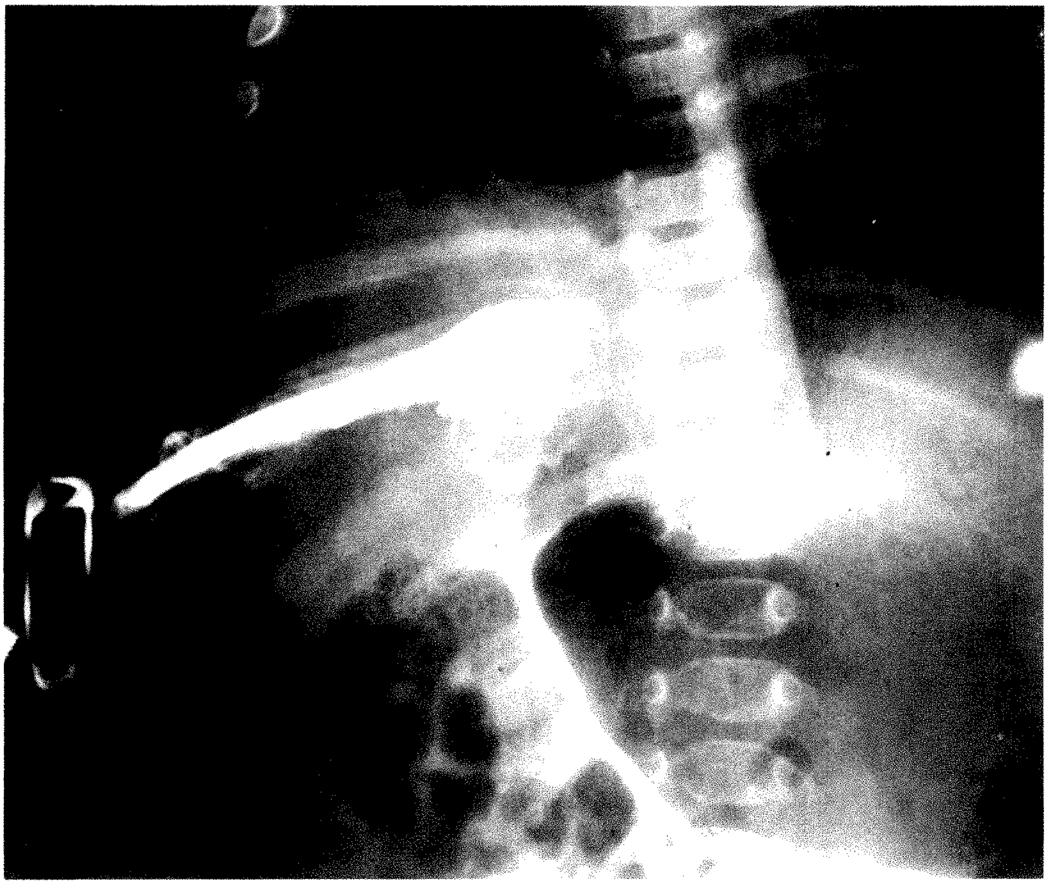

FIG. 3. Sinogram obtained ten days postoperatively, showing almost complete collapse of pseudocyst cavity.

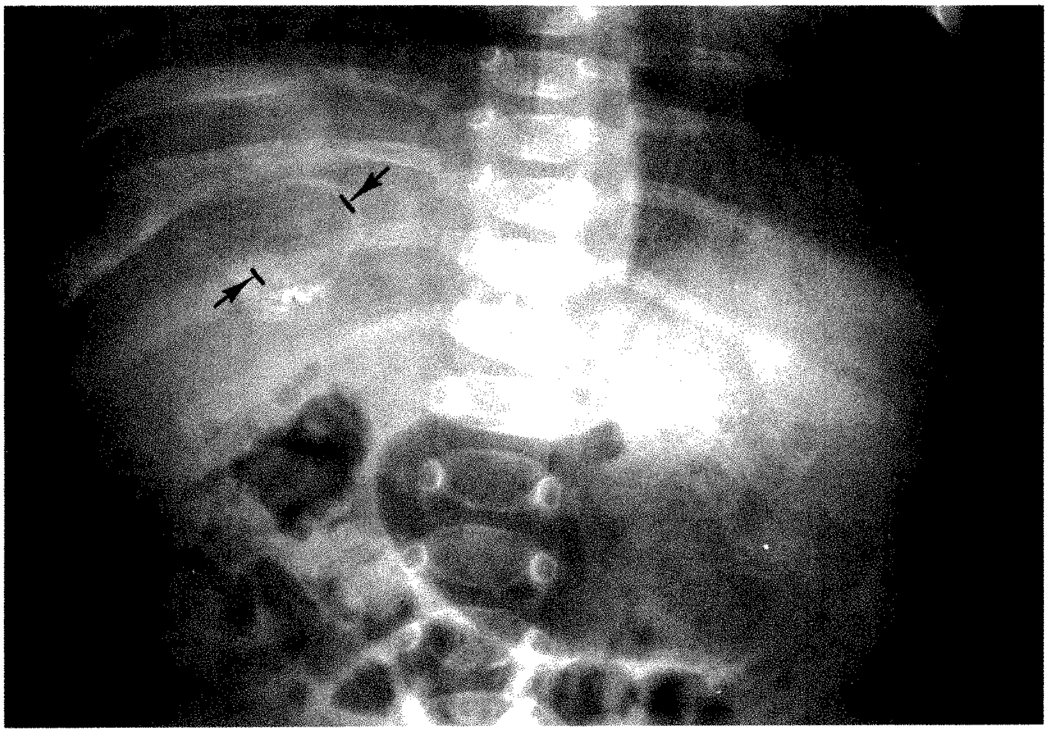

FIG. 4. Marked diminution in size of calcified mass is seen two weeks following surgery. Remodelling of tenth rib has begun.

sibly because of susceptibility of the enlarged gland to compression between the liver and spine.[7] Hemorrhage within the adrenal gland leads to necrosis of its tissue and distention of the gland within its capsule. Rupture of the hematoma may occur into either the retroperitoneal or peritoneal spaces. If rupture into the peritoneal cavity occurs, the clinical picture of shock and an acute abdomen is seen. When the hemorrhage is contained in the retroperitoneal space, symptoms related to the mass predominate. Jaundice, an unexplained drop in hemoglobin, or gastrointestinal symptoms due to compression of adjacent viscera may call attention to this lesion. Adrenal insufficiency is not usually seen.

Adrenal calcification is seen in various neoplasms (neuroblastoma, ganglioneuroma, virilizing tumors, and pheochromocytoma); familial xanthomatoses (Wolman's Disease); tuberculosis; echinococcal disease; Addison's Disease; and adrenal hemorrhage.[2] However, in solid tumors and these other conditions, the calcifications generally appear as amorphous, nodular masses within the substance of the glandular mass. Although it is possible for the calcification within a tumor to localize to the periphery, abnormal levels of endocrinologic excretory products are usually seen in such patients, helping to differentiate them from patients with benign cysts, in whom levels are usually normal or subnormal. Rim-like calcification within the abdomen can be seen with arterial aneurisms; hepatic, splenic, pancreatic, or renal cysts; dermoids; and renal tumors. These entities were excluded in our patient.

The apparent metastasis to rib in our patient made neuroblastoma a major differential diagnosis. The normal VMA and catecholamine levels, metastatic bone series, liver scan, bone marrow, surgical biopsies, and clinical course of the patient ruled out this diagnosis. Although the presence of "neuroblastoma in situ" has been reported in a neonatal adrenal cyst,[8] no mention of calcification or metastasis with this entity has been made, and its exact significance is unclear.

Failure to culture an organism from the cyst aspirate differentiates our patient from neonates with infected calcified cysts reported by Favara[4] and Van De Water and Fonkalsrud.[9] In the cases of neonatal pseudocysts following hemorrhage reported by Wagner[10] and Gross, *et al.*,[6] the cysts were bilateral in each instance. In no previously reported case of benign adrenal pseudocyst has extension into the thoracic region with destruction of a rib by pressure from the mass been noted.

Summary

The tenth case of a symptomatic adrenal cyst in an infant is reported. Although 3 previous case reports have described rim-like calcification of the cyst, none has shown extension of the mass into the thoracic region with resultant pressure erosion of a rib, mimicking metastatic disease. This unusual clinical picture, the pathogenesis of neonatal adrenal pseudocysts, the differential diagnosis, and the successful management of our patient are discussed.

References

1. Abeshouse, G. A., Goldstein, R. B. and Abeshouse, B. S.: Adrenal Cysts: Review of the Literature and Report of Three Cases. J. Urol., **81**:711, 1959.
2. Berdon, W. E. and Baker, D. H.: Radiographic Findings in Adrenal Disease in Infants and Children. N. Y. State J. Med., **69**:2773, 1969.
3. Cerise, E. J. and Hammon, J. W., Jr.: Adrenal Cyst. Surgery, **63**:903, 1968.
4. Favara, B. E., Akero, D. R. and Franciosi, R. A.: Adrenal Abscess in a Neonate. J. Pediatr., **77**:682, 1970.
5. Greiselius: Cited by Doran, A. H. G.: Cystic Tumor of Suprarenal Body Successfully Removed by Operation. Br. Med. J., **1**:1558, 1908.
6. Gross, M., Kottmeier, P. K. and Waterhouse, K.: Diagnosis and Treatment of Neonatal Adrenal Hemorrhage. J. Pediatr. Surg., **2**:308, 1967.
7. Kuhn, J., Jewett, T. and Munschauer, R.: The Clinical and Radiographic Features of Massive Neonatal Adrenal Hemorrhage. Radiology, **99**:647, 1971.
8. Tubergen, D. G. and Heyn, R. M.: In Situ Neuroblastoma Associated with an Adrenal Cyst. J. Pediatr., **76**:451, 1970.
9. Van De Water, J. M. and Fonkalsrud, E. W.: Adrenal Cysts in Infancy. Surgery, **60**:1267, 1966.
10. Wagner, A. C.: Bilateral Hemorrhagic Pseudocysts of the Adrenal Glands in a Newborn. Am. J. Roentgenol. Radium Ther. Nucl. Med., **86**:540, 1961.

Bacterial Endocarditis Associated with Colorectal Carcinoma

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THE PRESENCE OF ENDOCARDITIS has been described in association with a variety of malignant lesions.[1] Carcinoma of the colon and rectum has been reported in association with the nonbacterial thrombotic variety of the disease,[5] but rarely with bacterial endocarditis.[4] This report describes 3 patients treated for carcinoma of the colon or rectum, over a 9-month period, whose clinical picture was consistent with bacterial endocarditis.

Case Reports

Case 1. A 53-year-old man was admitted to another hospital with a one-month history of fever, weight loss, fatigue and general malaise. Two weeks prior to admission he noted the onset of diarrhea and rectal bleeding. Fever was subsequently noted daily to 39.4°C and the patient was admitted to the hospital. There was no previous history of heart disease. Physical examination revealed a Grade III/VI systolic ejection murmur heard best at the left sternal border. Electrocardiogram was compatible with incomplete right bundle branch block. CBC and urinalysis were within normal limits. The chest X-ray on admission was normal. Sigmoidoscopy revealed an ulcerative lesion on the posterior rectal wall at 7 cms. Biopsy of the lesion returned a diagnosis of well-differentiated adenocarcinoma. Five blood cultures obtained during the first 24 hours after admission were positive for Enterococcus. Upper GI series, intravenous pyelogram, oral cholecystogram, liver scan and bone survey were all normal. Cultures of the urine and sputum were negative. A diagnosis of bacterial endocarditis was made. On the basis of culture sensitivities and because of a history of penicillin allergy, a course of vancomycin therapy was begun. Fever elevations subsided within 3 days of therapy. Two weeks later the patient was transferred to our hospital where the following week abdomino-perineal resection of the lesion was performed. There was no evidence of metastatic disease on abdominal exploration. Microscopic examination of the specimen revealed penetration through the bowel wall with 11 examined nodes negative for adenocarcinoma. The patient continued on vancomycin therapy until his dicharge from the hospital 3 weeks later. The postoperative course was uneventful. Follow up examinations of the patient reveal no evidence of microembolic phenomena or recurrent bacteremia.

Case 2. A 36-year-old man was admitted to the hospital for fever of 3 months duration. Fevers had been noted as high as 39.4°C and were associated with shaking chills. His past medical history included a subtotal gastrectomy for bleeding peptic ulcer ten years prior to admission. There was no history of heart disease. On physical examination the blood pressure was 110/70 mm Hg, the pulse was 100 and the temperature was 38.8°C. Cardiac examination revealed no murmurs. Chest X-ray and electrocardiogram were both normal. Hematocrit was 36% with a reticulocyte count of 3.2%. The WBC was 8,100 with a differential within normal limits. Urinalysis on admission was normal. Six blood cultures over the first 24 hours after admission were positive for *Streptococcus salivarius*. Cultures of the throat grew normal flora, urine cultures were negative, and stool cultures were negative for enteric pathogens. A course of aqueous penicillin, 20 million units daily, was begun. One week after admission, the patient experienced an episode of crushing pain in the mid-epigastrium associated with palpitations. ECG revealed frequent PVC's and T wave inversions in II, III, and AVF. ECG changes reverted in 24 hours to normal. At this time splinter hemorrhages were noted in the right fifth digit. Two weeks later a murmur of aortic insufficiency was heard which increased in intensity over the next 2 weeks. Urinalysis at this time revealed 10–15 rbc/high power field and a routine Guaiac test of the stool was positive. A proctosigmoidoscopic examination was normal but a barium enema revealed a lesion in the distal portion of the ascending colon. Penicillin therapy was continued for a total course of 6 weeks at which time the patient underwent a right hemi-colectomy for carcinoma. There was no evidence of metastatic disease on abdominal exploration. Microscopic examination of the specimen revealed adenocarcinoma invading the submucosa with 22 examined nodes negative. Antibiotic therapy was continued until discharge from the hospital 2 weeks later. The postoperative course was uneventful. Follow up examinations of the patient reveal no evidence of recurrent bacteremia.

Case 3. An 83-year-old man was admitted to the hospital with

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a history of melenotic, diarrheal stools of 5 weeks duration. There had been a weight loss of 15 pounds during this period. Procto-sigmoidoscopy prior to admission was unremarkable but a barium enema revealed a sigmoid colon lesion and the patient was admitted to the hospital. There was no history of heart disease. On physical examination the pulse was 72, the blood pressure was 160/80 mm Hg, and the temperature was 37.4°C. A Grade IV/VI systolic murmur was heard best at the second left intercostal space and was noted to radiate to the neck. There was a palpable thrill. Admission CBC and urinalysis were within normal limits. ESR was 92 mm per hour. ECG revealed both right and left bundle branch block. Two days after admission the patient's temperature was elevated to 39.4°C. Chest X-ray revealed the development of a new right lower lobe infiltrate and right pleural effusion. The patient was noted to have developed petechiae of the soles, palms and soft palate. Blood cultures were negative during this period. Cultures of the urine, sputum, pleural effusion and spinal fluid were negative. Bronchoscopic examination was unremarkable. The patient subsequently developed a monocytosis of 21. A clinical diagnosis of bacterial endocarditis was made and Penicillin therapy was begun. The patient's fever returned to normal 48 hours after the institution of therapy. The chest X-ray cleared one week after therapy was begun. Therapy was continued for 6 weeks at which time the patient underwent an anterior resection of an annular carcinoma of the sigmoid colon. There was no evidence of metastatic disease on abdominal exploration. Microscopic examination of the specimen revealed transmural spread with secondary carcinoma in the surrounding adipose tissues. One of 12 examined nodes was positive for adenocarcinoma. Penicillin therapy was continued until discharge from the hospital 2 weeks later. The postoperative course was unremarkable. Follow up examinations of the patient reveal no evidence of recurrent bacteremia.

Discussion

The 3 patients reported presented with signs and symptoms of both bacterial endocarditis and carcinoma of the colon or rectum. A review of the literature has revealed only one previous report of a case with this association.[4] Endocarditis has long been recognized as frequently associated with other disease processes.[8] Non-bacterial thrombotic endocarditis has been emphasized as a well recognized cause of morbidity and mortality in patients with malignant tumors. Bryan,[2] in a review of 22 cases of nonbacterial thrombotic endocarditis found 2 cases associated with carcinoma of the colon and rectum. This form of endocarditis was found more frequently in association with malignant lesions of the pancrease, stomach and lungs. The presentation of these 3 patients differs from that of patients with colorectal carcinoma reported to have non-bacterial thrombotic endocarditis. The latter generally have far advanced disease with generalized wasting and evidence of circulatory stress and a clinical diagnosis of endocarditis is rarely made during life.

In Case 1 blood cultures repeatedly grew Enterococcus. *Enterococcal septicemia* has been reported in association with endocarditis after manipulation of the genito-urinary tract,[3,7] and following septic abortion.[6] Procto-sigmoidoscopic examination with biopsy of an infiltrative colorectal lesion may initiate bacteremia by a similar mechanism. In the case presented, however, procto-sigmoidoscopy was performed subsequent to the development of evidence of *Enterococcal bacteremia.*

Whether a causal relationship between the malignancy and endocarditis existed in these cases is speculative. Absence of a history of any known heart disease and failure to demonstrate any of the usual portals of entry for the infecting organisms, however, suggests that the concurrent development of the two diseases warrants further attention in the future. In particular, the existence of fevers of undetermined etiology in patients with carcinoma of the colon or rectum should direct attention to the possibility of a coexisting bacterial endocarditis. The experience presented suggests that definitive surgical treatment of a colorectal carcinoma may be undertaken once a clinical remission of an associated bacterial endocarditis has been achieved with the appropriate antibiotic therapy.

Summary

A report of 3 patients with carcinoma of the colon or rectum and bacterial endocarditis is presented. A review of the literature indicates that the previously reported association of these two diseases is rare. Fevers of undetermined etiology in patients with colorectal carcinoma should direct attention to the possibility of a co-existing bacterial endocarditis.

References

1. Barry, W. E. and Scarpelli, D.: Non-bacterial Thrombotic Endocarditis. Arch. Intern. Med., **109**:151, 1962.
2. Bryan, C. S.: Non-bacterial Thrombotic Endocarditis with Malignant Tumors. Am. J. Med., **46**:787, 1969.
3. Finn, J. J., Jr. and Kane, L. W.: Enterococcal Endocarditis as a Complication of Urologic Instrumentation. Proc. N. Engl. Cardiovas. Soc., 54, 1951.
4. McCoy, W. C. and Mason, J. M., III: Enterococcal Endocarditis Associated with Carcinoma of the Sigmoid: Report of a Case. J. Med. Assoc. Alabama, **21**:162, 1951.
5. McKay, D. G. and Wahle, G. H.: Disseminated Thrombosis in Colon Cancer. Cancer, **8**:970, 1955.
6. Mandell, C. L., Kaye, D., Levison, M. E. and Hook, E. W.: Enterococcal Endocarditis. Arch. Intern. Med., **125**:258, 1970.
7. Merritt, W. A.: Bacterial Endocarditis as a Complication of Transurethral Prostatic Resection. J. Urol., **65**:100, 1951.
8. Tompsett, R.: Bacterial Endocarditis. Changes in the Clinical Spectrum. Arch. Intern. Med., **119**:329, 1967.

Ureteral Obstruction Secondary to Aortic Femoral Bypass

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Ureteral injury resulting in obstruction or extravasation of urine is a serious and not infrequent complication of pelvic and abdominal surgery. There is a well recognized risk of injury to the ureter during radical operations for pelvic cancer and gynecological surgery. Thus, considerable care is taken during the procedure to avoid injury to this structure.

Ureteral obstruction secondary to untreated abdominal aneurysm was first reported by Goodwin and Schumacker in 1947.[4] Since then, there have been several additional reports of ureteral obstruction secondary to abdominal, iliac, or hypogastric artery aneurysms.[1,3,6–8] However, the obstruction of a ureter following reconstructive vascular surgery has not been a frequently reported complication.[2,5,9] The authors feel that it may be more common than recognized, since unilateral injury may lead to silent hydronephrosis and ultimate destruction of the kidney.

The following 4 cases are from 3 different institutions. They presented in a variable manner and represent various degrees of obstruction.

Case Reports

Case 1. J. C. A 63-year old white male was admitted to the hospital on February 26, 1968 with urinary obstructive symptoms. The patient complained of a poor stream, interrupted stream, and a feeling of not emptying the bladder. The patient denied any symptoms of vesicle irritation such as urgency and dysuria. There was no hematuria present.

Past history revealed that on November 11, 1967 the patient had surgery for a right aortofemoral bypass and a right lumbar sympathectomy performed. A dacron graft was placed between the proximal aorta and the femoral artery. There was no recognized ureteral injury. The patient did well postoperatively and was discharged in good health.

Physical examination revealed a healthy 63-year-old white male. The abdomen was soft and non-tender. There were no abnormal masses palpable. The scrotum contained two testicles normal in size and consistency. Prostatic examination revealed a prostate that was smooth and felt to be enlarged to 1+.

Laboratory data included a urinalysis with a pH of 5, specific gravity 1.021, negative for albumin and sugar. There were 3–5 white blood cells/hpf. Urine culture was negative. The blood urea nitrogen was 18 mgs. percent and a serum creatinine 0.8 mgs. percent.

An excretory urogram demonstrated delayed visualization with moderate hydronephrosis and hydroureter of the right collecting system (Fig. 1). The ureter could not be visualized beyond the second sacral segment.

Cystoscopic and retrograde examination was then carried out; multiple urethral strictures, median bar hyperplasia and obstruction of the right ureter just below the pelvic brim was demonstrated (Fig. 2).

On March 5, 1968 the patient was returned to the operating room where the urethral strictures were dilated and transurethral resection of the prostate was carried out.

On March 15, 1968 the patient was operated on transperitoneally. The right ureter was dissected free from the structures surrounding it and was found to be encased in dense thick fibrous tissue passing underneath the femoral graft and compressed between the patient's right common iliac artery and the limb of the dacron prosthesis. The ureter was dissected free from the graft, divided and then re-anastomosed in front of the graft. A tube which had been bivalved was inserted as a splint with the lower limb passing through the anastomosis and into the bladder. The omentum was then brought down and placed between the ureter and the graft to prevent the ureter from becoming adherent to the graft.

The patient made an uneventful recovery. The T tube was removed after 10 days. The patient has had no further difficulty and repeat intravenous pyelograms at the end of 6 months showed prompt excretion of contrast material with considerable diminution of the hydronephrosis.

Case 2. L. F. A 56-year-old white male was seen on July 17, 1969. He was admitted with the urinary obstructive symptoms of hesitancy, decreased urinary stream, interrupted stream and a

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feeling of not emptying the bladder. In addition, there were symptoms of urgency, frequency, but no dysuria.

Past history disclosed acute urinary retention in 1963. X-rays of the kidneys revealed a non-functioning left kidney one month prior to admission. A bilateral aortic femoral bypass graft had been inserted on January 15, 1969.

On physical examination there was a grade III/VI systolic murmur heard best at the base of the third intercostal space on the left. The heart tones were regular. Peripheral pulses on the right were greater than the left. The genitalia were normal; the prostate +— and benign.

Laboratory results: The urinalysis: pH 5; specific gravity 1.010; albumin 1+; 50–100 white blood cells/hpf; 8–10 red blood cells/hpf; acid phosphatase 2.1 unit. The blood urea nitrogen was 52 mgs. per cent. The serum creatinine was 1.7 mgs. per cent.

Cystoscopic examination showed benign prostatic hypertrophy and a retrograde pyelogram complete obstruction within the true pelvis (Fig. 3).

On July 29, 1969 the patient was operated on transperitoneally. The ureter was found encased in dense fibrous tissue between the graft and the common iliac vessel. The periureteral fibrosis extended into the true pelvis. The proximal portion of the ureter was dilated. A nephrectomy and partial ureterectomy was done. The postoperative course was unremarkable.

Case 3. F. H. A 63-year-old white male was seen on July 27, 1970 with urinary obstructive symptoms of hesitancy, decreased urinary stream, and an interrupted urinary stream. In addition there was a history of urgency, frequency, and dysuria but no hematuria.

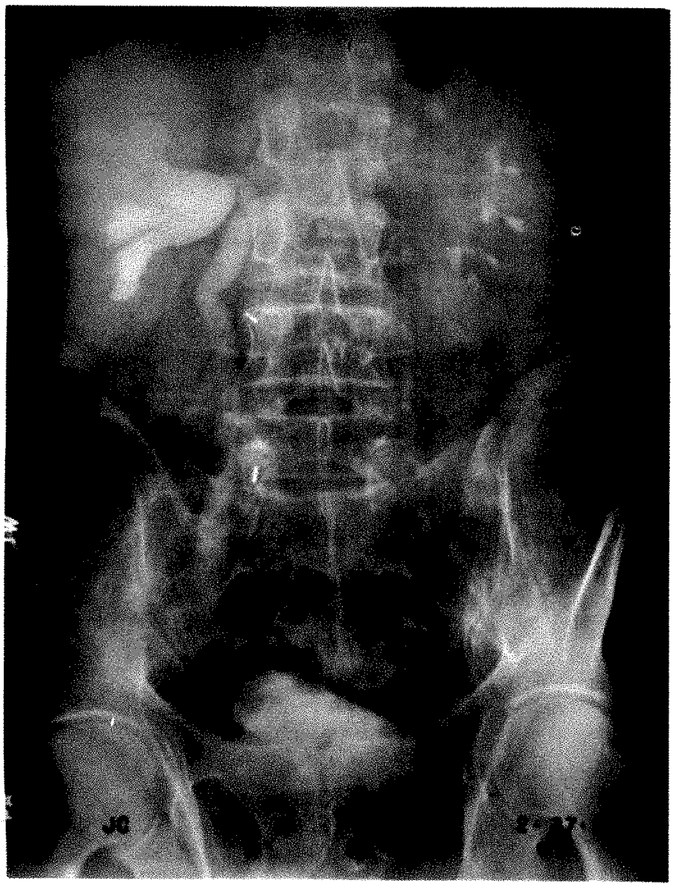

FIG. 1. J. C. Intravenous pyelogram showing obstruction of the right ureter with hydroureter and hydronephrosis.

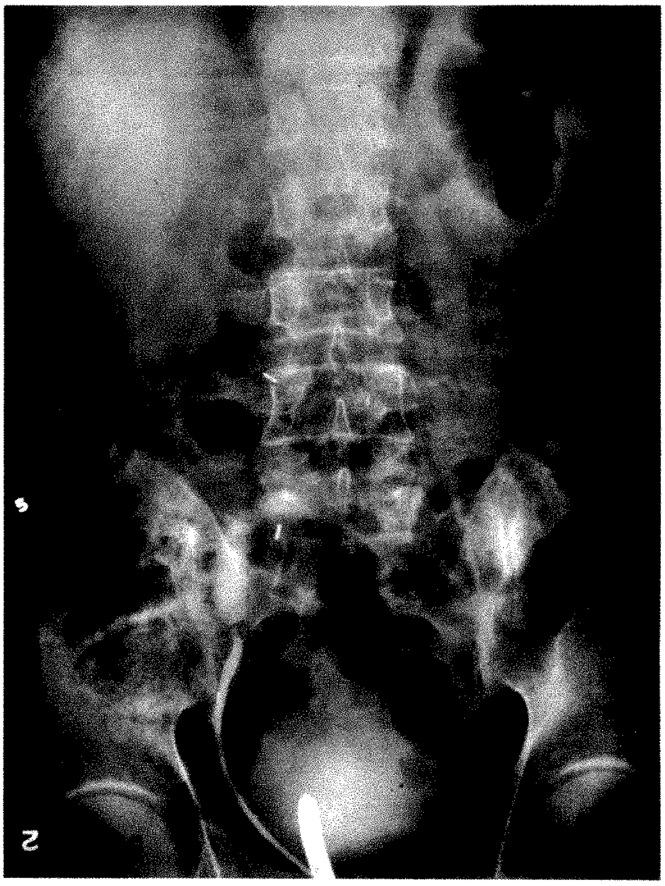

FIG. 2. J.C. Retrograde pyelogram showing site of obstruction, right ureter.

Past history revealed gonorrhea with resultant urethral stricture. A bilateral aortic femoral bypass operation had been done on May 20, 1970 for vascular obstruction.

The physical examination was unremarkable. There were well-healed scars from the previous surgery. The genitalia were normal and the prostate was +— and benign to palpation.

Laboratory results revealed 100,000 colonies of enterococcal strep. The serum creatinine 1.7 mgs. per cent and the acid phosphatase 0.56 units. Intravenous pyelograms demonstrated pyelocaliectasis and ureterectasis on the right down to the pelvic brim. No contrast material was noted below the site of obstruction (Fig. 4). A delayed film showed good drainage (Fig. 5).

A cystoscopy and retrograde pyelogram were done. The urethra contained multiple strictures with the smallest calibrating at a No. 16 French. An internal urethrotomy was done. A No. 6 French ureteral catheter was passed 20 cms. up the right ureter and urine was collected for culture and sensitivity which showed enterococcal strep. A bulb ureterogram and right oblique film showed the ureter to be anterior to the graft. (Fig. 6). The patient was treated with Nalidixic Acid and the infection cleared.

The patient was seen on October 13, 1970 voiding with a good urinary stream. Urine culture was negative. A repeated intravenous pyelogram showed no change.

Case 4. R. J. A 62-year-old white male was seen on February 25, 1969 with a 4-month history of right lower chest pain. There were no genitrourinary symptoms.

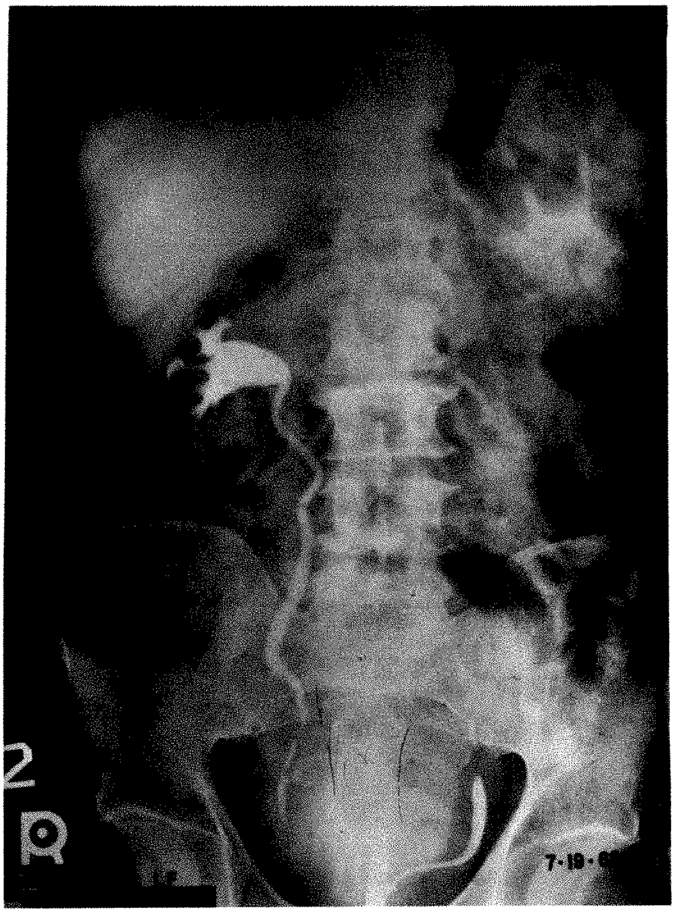

FIG. 3. L.F. Retrograde pyelogram showing complete obstruction left ureter.

Past history: On April 13, 1967 the patient had an aneurysmectomy repaired by a Teflon bifurcation graft extending from just below the renal arteries to the femoral arteries. An intravenous pyelogram done at that time was normal.

Physical examination revealed tenderness of the right flank to palpation and was otherwise unremarkable. The genitalia were normal and the prostate +— and benign.

Laboratory results: The blood urea nitrogen was 20 mgs. per cent. Urine for culture and sensitivity was negative. The serum creatinine was 1.0 mgs. per cent.

A retrograde pyelogram revealed obstruction to the right ureter at L4 (Fig. 7). No further treatment was carried out. The patient was last seen on February 9, 1971 having passed a blood clot. The intravenous pyelogram showed marked ureteral and pyelocaliectasis on the right (Fig. 8). The blood urea nitrogen was 23 mgs. per cent and a urine culture was negative.

Discussion

Although ureteral obstructions as a complication of aortic femoral bypass has not been reported frequently, we feel there is reason to believe that it occurs more frequently than recognized.

In 3 of our 4 cases the presenting complaints were referrable to the lower urinary tract and, indeed, the 3 patients had lower urinary tract pathology; i.e., urethral stricture and benign prostatic hypertrophy. The ureteral obstruction was found only because intravenous pyelograms are an integral part of evaluating lower urinary tract complaints.

Ureteral obstruction may not be recognized or produce symptoms if the proximal urine is not infected. Thus, silent hydronephrosis and hydroureter may lead to complete destruction of the kidney as in our second case. Such findings would lead one to raise the question of the routine use of intravenous pyelograms after aortic femoral or aortic iliac grafts.

Only passing reference is made to the ureter relative to the graft in standard surgical text books of vascular disease. From our experience and others,[2,9] it would seem essential that the iliac limb of the graft be tunneled digitally under the posterior parietal peritoneum and the anterior surface of the iliac artery. In so doing the ureter is reflected anterior to the graft with the posterior peritoneum to which it is attached. This would avoid the situation which was present in 2 of our cases, where we found that the ureter was mechanically compressed by the rigid graft and surrounded by periureteral fibrosis which lead to the obstruction.

Whenever possible the urinary tract should be recon-

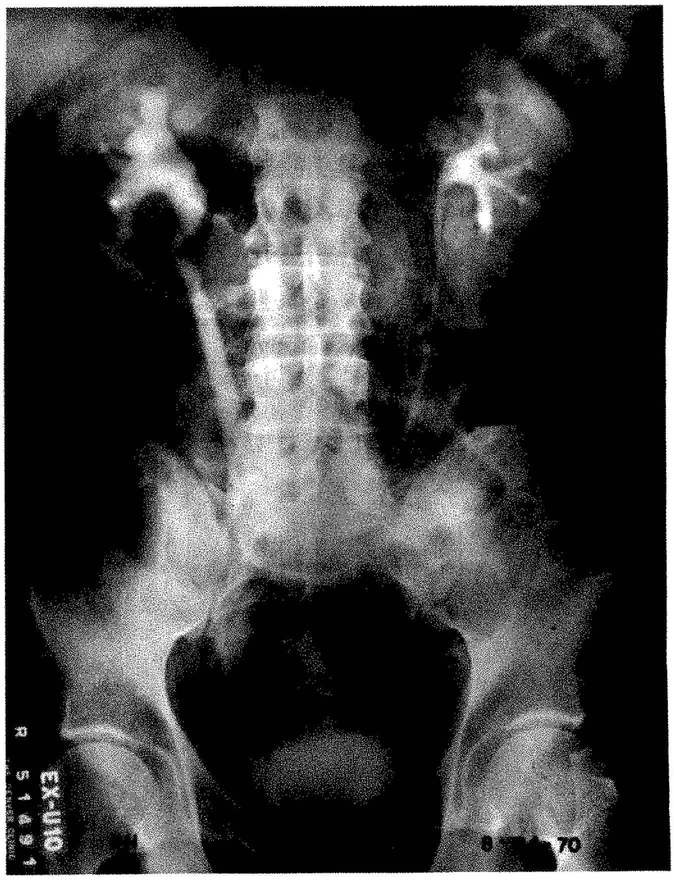

FIG. 4. F.H. Intravenous pyelogram showing pyelocaliectasis and ureterectasis on the right.

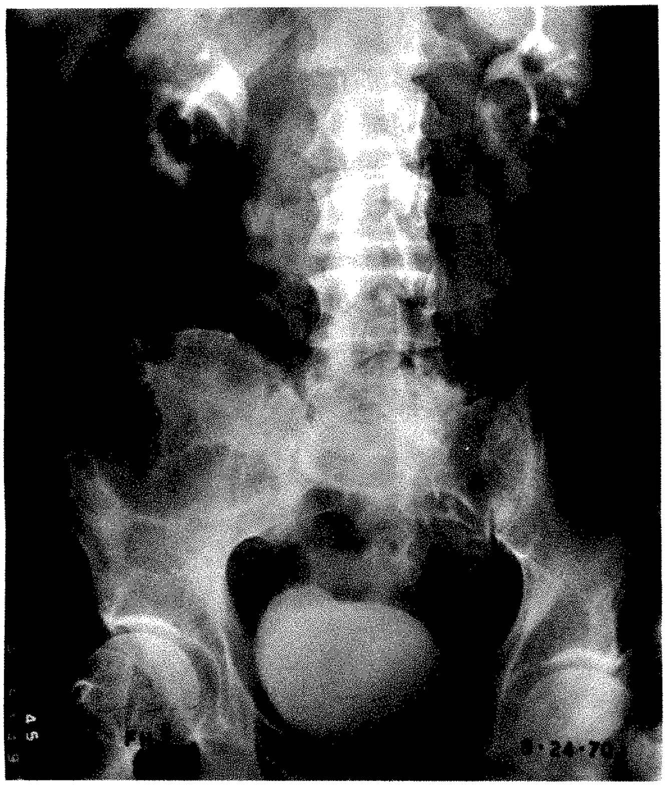

FIG. 5. F.H. Delayed intravenous pyelogram of Figure 4 showing good drainage.

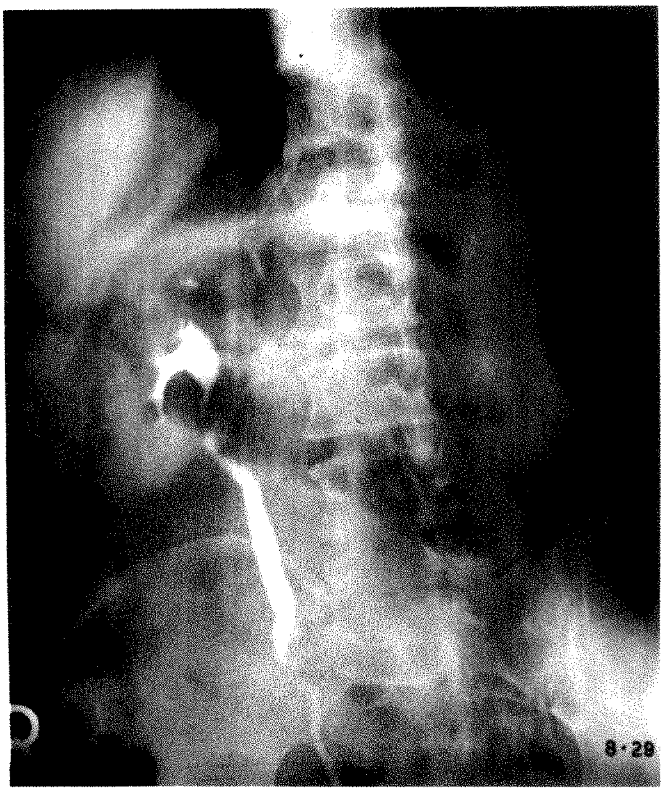

FIG. 6. F.H. Right bulb ureterogram and right oblique film showing the ureter to be anterior to graft.

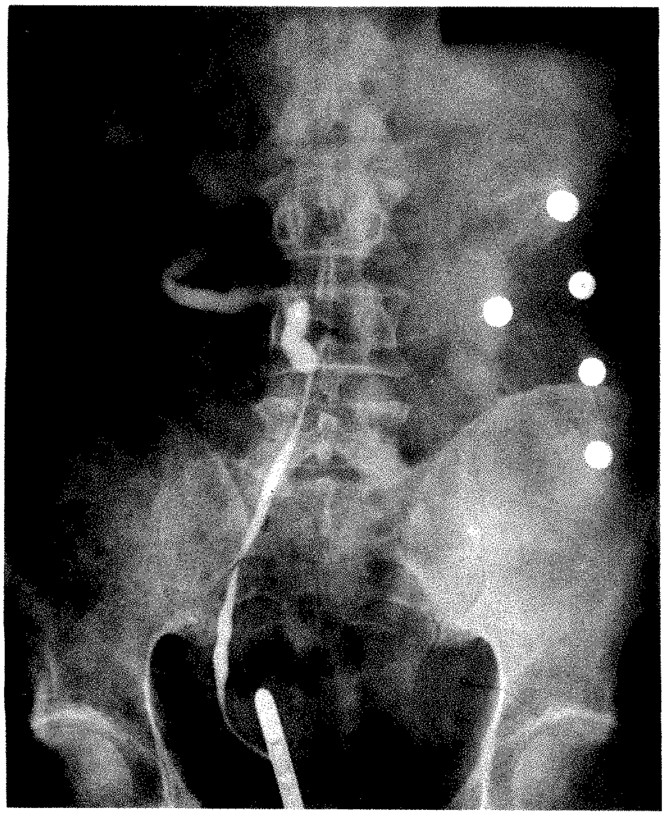

FIG. 7. R.J. Right retrograde pyelogram revealing obstruction to right ureter.

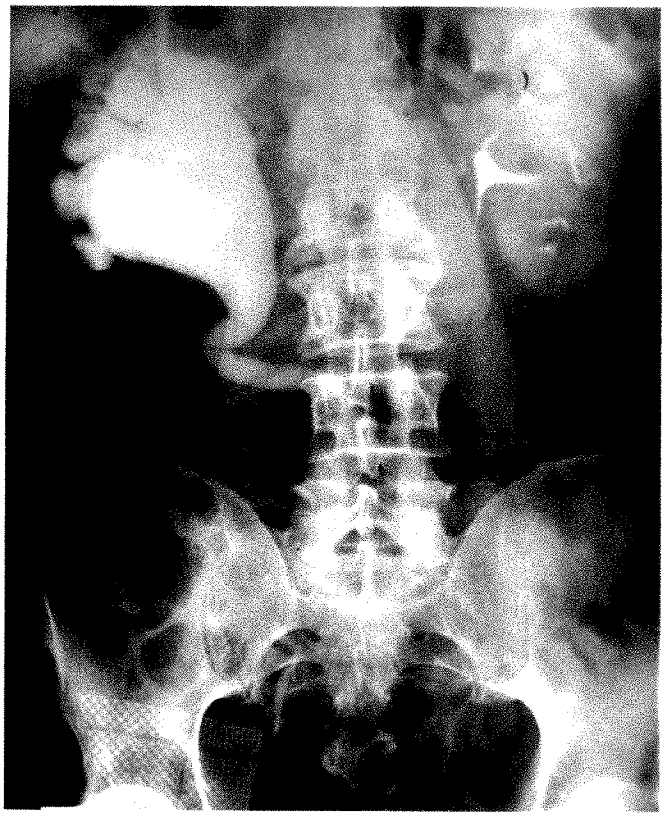

FIG. 8. R. J. Intravenous pyelogram showing obstruction with severe ureterectasis and pyelocaliectasis on the right.

structured by adequately mobilizing the ureter, spatulating the divided ends and carefully anastomosing the ends using fine interrupted sutures of absorbable material. Proximal drainage is essential to avoid extravasation of urine at the anastomotic site. Extravasation of urine around the graft leads to an increase in fibrous reaction and further stricture formation. It also might lead to infection around the graft with lethal complications for the graft and possibly the patient.

Summary

We have presented 4 cases of various degrees of obstruction to the ureter as a result of reconstructive vascular surgery; i.e., aortic femoral bypass.

The manner in which they presented would suggest that the complication is more common than suspected. It would appear that it is essential that the ureter be placed anterior to the graft during the procedure to avoid compressing the ureter between the common iliac artery and the limb of the aortic femoral bypass prosthesis.

Treatment by division and reconstruction of the ureter with transposition in front of the graft is preferred treatment whenever possible.

References

1. Albers, D. D., Bettaglio, H.: Ureteral Obstruction from an Unsuspected Aortic Aneurysm—Case Report. J. Urol., **85**: 249, 1961.
2. Bernard, L.: Ureteral Obstruction Following Aortofemoral Bypass Grafts. Surg., **59**:918, 1966.
3. Dewund, J. H., et al.: Aortic Aneurysm Causing Bilateral Ureteral Obstruction—Report of a Case. J. Urol., **74**:78.
4. Goodwin, W. E., Schumacker, H. B. Jr.: Aneurysm of the Hypogastric Artery Producing Urinary Tract Obstruction—Report of a Case. J. Urol., **57**:839, 1947.
5. Jacobson, M. E., et al.: Ureteral Obstruction as a Late Complication of Abdominal Aneurysm Resection. J. Kans. Med. Soc., **63**:516, 1962.
6. Kornfield, H. J., Jacobson, M. E.: Ureteral Obstruction, an Unusual Complication of Iliac Aneurysm. J. Kans. Med. Soc., **59**:252, 1958.
7. Labardini, M. D., R. W. Dow: Primary Mycotic Aneurysm of Right Common Iliac Artery. Arch. Surg., **96**:373, 1968.
8. Schumacker, H. B. Jr., Garrett, K.: Obstructive Uropathy from Abdominal Aortic Aneurysm. Surg. Gynecol. Obstet., **100**:758, 1955.
9. Thomford, N. R., Dorfman, L. F.: Ureteral Obstruction Caused by an Aortofemoral Bypass Prosthesis. Surg., **115**:394, 1968.

Spontaneous Intraspinal Hemorrhage Causing Paraplegia:

A Complication of Heparin Therapy

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PARAPLEGIA RESULTING FROM SPINAL EPIDURAL HEMATOMA as a complication of anticoagulant therapy has been reported by various authors.[2,4,6,15,17,20] It is essentially a curable entity if recognized and treated promptly. Comprehensive research of the English literature failed to cite a case of paraplegia due to subpial, subarachnoid and subdural hematoma. Cloward and Yuhal[2] did report a case of paraplegia developing subsequent to Dicumarol therapy, the etiology being extensive epidural, subdural and subarachnoid hemorrhage confirmed surgically. Notable, however, there was no subpial hemorrhage. The purpose of this paper is to describe such an instance of paraplegia developing as a complication of Heparin therapy and verified at operation.

Case Report

A 29-year-old Negro male was admitted to Mercy Hospital on January 22, 1972, with a gunshot wound of the right thigh. No neurological deficit was reported on admission. A right femoral arteriogram was performed which revealed a laceration and traumatic aneurysm of the distal superficial femoral artery on the right side. Under spinal anesthesia, repair of the right superficial femoral artery in Hunter's canal was done. Apparently, spinal anesthesia was carried out via an atraumatic puncture at L_{4-5} with a 25 gauge needle and tetracaine 10 mg and adrenalin 0.5 mg in 2.5 ml were administered intrathecally. Postoperatively, the patient did well and was heparinized. Six thousand units of heparin were given every 4–6 hours and the Lee-White clotting time was 18 minutes 12 hours postoperatively.

The patient did well until 40 hours after surgery when he began to complain of severe pain in the back. Over the ensuing few hours, incontinence of bowel and numbness of both lower extremities were noted. Subsequently, progressive paraparesis developed and emergency neurosurgical consultation was requested. At this point, 9 hours after the onset of severe back pain, and 49 hours after the initial surgery, the patient was found to be paraplegic with an L_1 sensory level bilaterally. In addition, there was areflexia of the lower extremities and urinary retention necessitating catheter drainage. Dorsalis pedis and posterior tibial artery pulsations were present bilaterally. Emergency myelography was then carried out with the initial attempt being an L_5–S_1 puncture which yielded old, dark, unclotted blood. Thereupon, it became necessary to introduce via a lateral C_1–C_2 puncture, 3cc of Pantopaque, revealing bloody CSF and an incomplete block at D_{5-6} and a total block at D_{11} (Fig. 1). Under general anesthesia, laminectomy of the dorsal spine from D_5 to L_1 was carried out. The dura was found to be tense and bluish in color. No pulsations were seen. After an incision was made in the dura, old, dark blood emanated from the opening, which was estimated at 20cc. After the subdural blood had been removed, the spinal cord began to pulsate. As the arachnoid was opened, blood tinged CSF came out. A subpial collection of blood was seen from D_{10} to D_{12}, with maximal swelling at this level. The conus medullaris was pushed posteriorly against the dura and as the nerve roots were carefully retracted, old, dark blood came welling up from below and its consitency was identical with that obtained from the initial lumbar puncture attempt at L_5–S_1 for myelography. Approximately 20–25 cc of subarachnoid fluid was removed in this manner. A French catheter was then passed subdurally with ease indicating that no block remained. Ultimately, under the microscope, the area of subpial hemorrhage was visualized and no abnormal vasculature could be seen to indicate the site from which the hemorrhage had occurred. One half cm longitudinal incision was made in the pia allowing a further increment of spinal cord expansion. A fascia lata dural graft was fashioned and sutured into place with 4–0 silk interrupted sutures, and the incision was closed without drainage in multiple layers with stainless steel wire.

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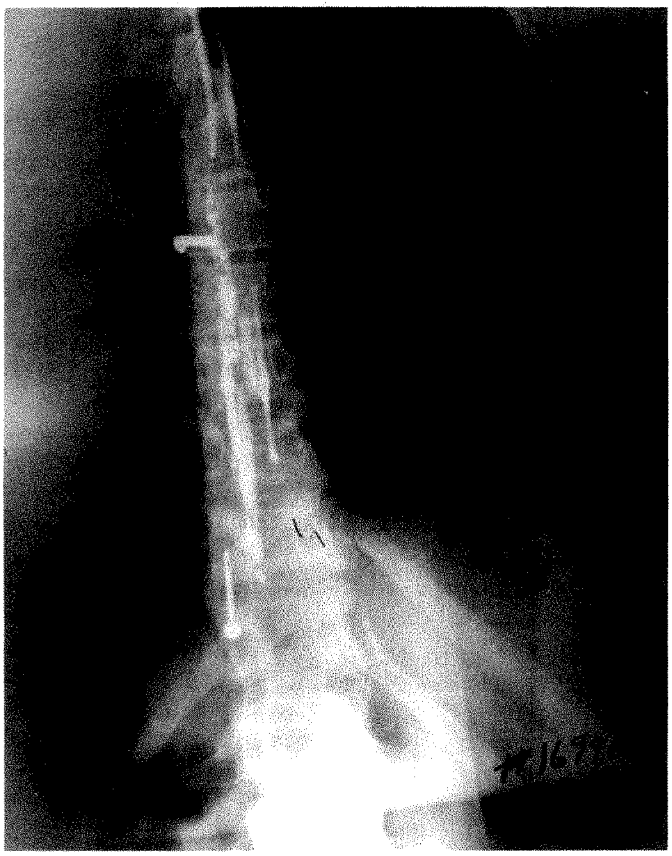

FIG. 1. Introduction of 3 cc of pantopaque into subarachnoid space via a lateral C_1–C_2 puncture revealed an incomplete block at D6 and total block at D11 level.

Ten hours postoperatively, flexion and extension movements of the toes and ankles were seen bilaterally, and the sensory level had dropped to L_2. Forty-eight hours after decompression, antigravity contractions of hamstrings, iliopsoas, and quadriceps muscles were noted. Sensation to pin was now present down to L_5. Three weeks following surgery, bowel and bladder control were regained. The patient was reevaluated neurologically while on the rehabilitation service. Three months later, the patient was now ambulating with the help of Lofstrand crutches. He could rise from the chair unassisted, but still had some weakness in hip extensors and hip flexors. The remainder of the musculature in the lower extremities was almost normal in strength and tone. S_3–S_5 hypalgesia, along with variable loss of vibratory position and two point discrimination persisted. The abdominals and deep tendon reflexes were absent. Extensor plantar responses were not elicited.

Comments

Spontaneous non traumatic epidural hematoma was first reported by Jackson in 1869, until 1971, over 50 cases had been reported. Markham, Lynge and Stahlman[9] described this syndrome of spontaneous spinal epidural hematoma and reviewed 49 cases. Most of the reported cases were acute or subacute in onset. In all cases, hematoma was in the region of the spinal cord except in one case of Svien,[19] one case of Pomme,[11] and one case of Schultz.[14] In these cases, the hematoma was localized in the region of the cauda equina. The only chronic cases reported by Boyd, *et al.*[1] and Harris,[5] and the clot in these cases was also located in the region of cauda equina. Only two cases of chronic subdural hematoma of the spinal cord have been reported, one by Rader[12] and one by Stewart, *et al.*,[16] indicating its rarity. In both cases, there was a definite history of trauma to the spinal axis with involvement of thoracic segments.

Spontaneous hemorrhage is a well-known complication of anticoagulant therapy. Jick, *et al.*,[7] while discussing the efficacy and toxicity of Heparin, mentioned the possibility of cerebral hemorrhage. Susens[18] reported 2 cases of femoral nerve entrapment secondary to Heparin therapy. Spontaneous spinal epidural hematoma in patients on anticoagulant therapy has already been alluded to. Schiller, *et al.*,[13] discussed surgical risks in a hemophiliac and reported a case of spinal subdural hematoma. Harik[4] documented a second case of spontaneously remitting spinal epidural hematoma.

Our case fits well into the syndrome of spontaneous spinal epidural hematoma, first described by Winer, *et al.*,[20] and subsequently reported by Markham, *et al.*,[9] Acute back pain, rapidly progressive spinal cord and nerve root deficit usually with a complete spinal block and brownish pigment in the spinal fluid precipitated usually by straining at stool, micturition, bending forward, turning in bed, lifting, and even sneezing. Symptoms during sleep occur in some, (cases #22, 36, 38, 42, 47 as compiled by Markham[9]). In most cases, profound paraparesis is seen within 3 hours, although it varies from 20 minutes to 10 days.[20]

Various postulates have been put forth to explain spontaneous intraspinal bleeding. Cube[3] stated that in 13 of 19 cases which he reviewed, bleeding arose from an epidural hemangioma. Lowery[8] in his 3 cases of spontaneous epidural hematoma, could not visualize a hemangioma at the time of surgery. Of course, the patients on anticoagulant therapy have a much greater incidence of bleeding.[7] Valslava maneuver and increased venous pressure could rupture small valveless venules in the epidural space. Intraspinal hemorrhage and paraplegia following lumbar puncture has been documented in patients on anticoagulant therapy.[10] In our case, we postulate that the source of bleeding was in the area of D_{10-12} where a subpial collection of blood was seen. Though no arteriovenous malformation angioma or any other vascular anomaly *per se* was seen at operation, a cryptic vascular anomaly could have been the source of bleeding which was acute in onset and leaked into the subarachnoid and subdural spaces. The patient's maximum deficit after the onset of symptoms, residual neurological deficit at the time of discharge, sensory level at L_1 before surgery and complete block at D_{11} will all point to the level of the hemorrhagic lesions between D_{10-12}. Acute onset of back pain prior to the development of neurologic symptoms for no apparent cause, supports the postulate that the intraspinal bleeding was spontaneous and that heparin therapy was an additive factor. Although intraspinal hemorrhage has been reported from lumbar puncture in patients on anticoagulants,[10] we doubt this etiology in this case because of the following reasons. Lumbar puncture was done with #25 gauge needle at a time when the patient was not on anticoagulants. The site of puncture was at L_{4-5} which was distant from the site of the lesion found at operation, and finally, no symptoms or neurological deficit was noted immediately following surgery and for a considerable period after.

We are reporting this unusual case of subdural, subarachnoid and subpial hematoma to stress: 1) Prompt recognization of the syndrome of spontaneous intraspinal hematoma. 2) Immediate surgical decompression of the hematoma, since the longer the delay in surgery after the onset of symptoms, the less likely are the chances of recovery of good function. 3) The C_{1-2} puncture in cases of spinal canal block is valuable and its safety has been confirmed repeatedly during many percutaneous cordotomy procedures over 4-5 year period.

Summary

The literature on spontaneous intraspinal hematoma has been reviewed, and an unusual case of spontaneous intraspinal hematoma involving subpial, subarachnoid and subdural spaces has been reported. Prompt recognition of the syndrome of intraspinal hematoma, and immediate surgical decompression has been stressed. The value of C_{1-2} puncture in cases of intraspinal block is mentioned.

References

1. Boyd, H. R. and Pear, B. L.: Chronic Spontaneous Spinal Epidural Hematoma. J. Neurosurg., 36:239, 1972.
2. Cloward, R. B. and Yuhl, E. T.: Spontaneous Intraspinal Hemorrhage and Paraplegia Complicating Dicumarol Therapy—Case Report. Neurology, 5:600, 1955.
3. Cube, H. M.: Spinal Extradural Hemorrhage. J. Neurosurg. 19:171, 1962.
4. Harik, S. I., Raichle, M. E., and Reis, D. J.: Spontaneously Remitting Spinal Epidural Hematoma in a Patient on Anticoagulants. New Engl. J. Med., 284:1355, 1971.
5. Harris, M. E.: Spontaneous Epidural Spinal Hemorrhage. Amer. J. Roentgenol. 105:383, 1969.
6. Jacobson, I., MacCabe, J. J., *et al.*: Spontaneous Spinal Epidural Hemorrhage during Anticoagulant Therapy. Brit. Med. J., 1:522, 1966.
7. Jick, H., Slone, D., *et al.*: Efficacy and Toxicity of Heparin in Relation to Age and Sex. New Engl. J. Med., 279:284, 1968.
8. Lowrey, J. J.: Spinal Epidural Hematomas, Experience with Three Patients. J. Neurosurg., 16:508, 1959.
9. Markham, J. W., Lynge, H. N. and Stahlman, G. E. B.: The Syndrome of Spontaneous Spinal Epidural Hematoma—Report of Three Cases. J. Neurosurg., 26:334, 1967.
10. Phelps, E. T.: The Dangers of Dicumarol Therapy. Med. Clin. North Am., 34:1791, 1950.
11. Pomme, B., Montrieul, B. and Girard, J.: Hematome Extradural Lomboire Spontane. Revue Neurol. 101:69, 1959.
12. Rader, P. J.: Chronic Subdural Hematoma of the Spinal Cord. New Engl. J. Med., 253:374, 1955.
13. Schiller, E., Neligen, G. and Budtz-Olson, O.: Surgery in Hemophilia—A Case of Spinal Subdural Hematoma Producing Paraplegia. Lancet, 842, Nov. 1948.
14. Schultz, E. C., Johnson, A. C. and *et al.*: Paraplegia Caused by Spontaneous Spinal Epidural Hemorrhage. *J. Neurosurg.*, 10:608, 1953.
15. Spurny, O. M., *et al.*: Spinal Epidural Hematoma during Anticoagulant Therapy. Arch. Intern. Med. 114:103, 1964.
16. Stewart, D. H., and Watkins, S. E.: Spinal Cord Compression by Chronic Subdural Hematoma, Case Report. J. Neurosurg., 31:80, 1969.
17. Straun, R. E.: Spinal Epidural Hematoma in Patients on Anticoagulant Therapy. Ann. Surg., 159:507, 1964.
18. Susens, G. P.. Hendrickson, C. G., *et al.*: Femoral Nerve Entrapment Secondary to a Heparin Hematoma. Ann. Intern., Med., 69:575, 1968.
19. Svien, H. J., Adson, A. W. and Dodge, H. W., 3rd.: Lumbar Extradural Hematoma—Report of a Case Simulating Protruded Disc Syndrome. J. Neurosurg., 7:587, 1950.
20. Winer, B. M., Horenstein, S. and Starr, A. M.: Spinal Epidural Hematoma during Anticoagulant Therapy. Circulation, 19:735, 1959.

Simultaneous Distribution Rate and Dilution Volume of Bromide-82 and Thiocyanate in Body Fluid Overload:

Experimental and Clinical Correlation

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THE BODY is composed of a large amount of water, mostly intracellular, with the remainder located extracellularly. Dependent upon the tracer substance used for its measurement, extracellular fluid volume comprises 15–20% of total body weight. This extracellular fluid compartment is in turn made up of a myriad of smaller compartments and pools. These include synovial fluid, cerebral spinal fluid, lymph, transcellular fluid of of the gastrointestinal tract, plasma, intraocular fluid, and interstitial fluid. The relatively wide range in reported extracellular fluid compartment size doubtless exists because the substances used for measuring this fluid compartment do not equilibrate equally in all the smaller component compartments and pools. Each tracer substance used to measure extracellular fluid volume has, therefore, exhibited its own characteristic advantages and disadvantages allowing little reliable comparison between substances.

Some of the inert tracer substances utilized for measuring extracellular fluid volume have included: sucrose,[11] inulin,[12,13] stable bromide,[36,40] thiosulfate,[6] and thiocyanate.[8,21,34] For many years, it was accepted that sodium thiocyanate permitted the closest estimation of functional extracellular fluid volume. However, in 1946, Overman[27] noted that febrile states, specifically those associated with malaria, apparently increased cellular permeability, resulting in thiocyanate volumes approaching the volume of total body water.

Attention was then directed from inert substances to the newer radioactive tracers. Some of the tracers utilized for measurement of extracellular fluid volume have included: sodium-24,[1,20] chloride-38,[41] chloride-36,[10] sulfate-35,[28,32,38] and bromide-82.[19,23–26] Based upon the early work of a number of investigators[5,17,18,33,37,39,40] with stable bromide, a solid foundation was laid for utilizing the newer radioactive isotope, bromide-82 (^{82}Br). Moore his associates[23,25,26] employed ^{82}Br and concluded the distribution of this tracer substance to be a specific and accurate estimation of functional extracellular fluid volume. Thus in recent years, ^{82}Br has become one of the most popular tracer substances used in determining body fluid composition in health and disease.

Little basic information has been published comparing the more widely used inert tracer, thiocyanate (SCN), with the more widely used radioactive tracer, bromide-82 (^{82}Br). Minimal investigation to determine the differences or similarities under specific clinical or experimental conditions has been performed for these 2 extracellular fluid volume tracers.

In addition, analysis of the exponential dilution curves of ^{82}Br and SCN has demonstrated in selected patients useful information concerning fluid distribution and kinetics.[3,29] However, most of this research has been limited to ^{82}Br, and little work has been directed at comparison of the exponential dilution curves of ^{82}Br and SCN under the same clinical conditions.

Large extracellular fluid shifts have been demonstrated in situations of fluid overload such as that following open heart surgery.[3,4,7,9,,28,30] Limited investiga-

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tions into other conditions of fluid overload have been reported,[15,22,31] but again, information comparing ^{82}Br and SCN under the same conditions is lacking. Correlation of these overload clinical problems with controlled investigations in the experimental laboratory might shed further light on interpretation and application of fluid volume measurements.

The present report is concerned with: 1) the comparison of ^{82}Br and SCN methods of measurement of extracellular fluid under experimental overload conditions; 2) the analysis of exponential dilution curves of ^{82}Br and SCN; and 3) correlation of these data with selected clinical measurements.

Materials and Methods

Preparation of Animals

Healthy mongrel dogs weighing 14–29 kg. were used. Only male animals were utilized to avoid female hormone influences and possible undetected pregnancy. All animals were negative for microfilaria. The dogs were placed under light pentobarbital anesthesia during the experiments and were turned from side to side hourly to prevent hypostatic pneumonia. Penicillin and streptomycin prophylaxis was employed throughout each period of investigation.

Tracer Substances

The tracers used for dilution measurements were injected intravenously from calibrated syringes as follows:

1. Deuterium oxide, 20 ml of 99.5% in 0.85% NaCl.
2. Evans blue dye, 1 ml of 0.5% solution.
3. ^{82}Br as NaBr, 60–100 microcuries in 10 ml of 0.85% NaCl.
4. Thiocyanate as NaSCN, 10 cc of 5% solution.

Injection and Sampling Techniques

The animal was weighed on the morning of study. The bladder was catheterized under sterile conditions and the excreted urine was shunted into the venous system by means of an intravenous forearm line, pump, and filter (Fig. 1). The urinary excretion variable was thereby eliminated. After baseline blank samples and hematocrits were obtained, the tracers were injected through an intravenous line and washed in with 50 ml of 5% dextrose in water. Femoral venous blood samples were drawn at 5, 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, and 300 minutes. After the last blood sample was obtained the animal was returned to his cage.

Experimental Design

Each animal served as his own control. One liter of Ringer's lactate solution was administered to insure a well-hydrated animal the day before the control study. After an overnight fast (water *ad lib*), the control study was performed over a five-hour period as described above.

The fluid overload experiment in each animal was performed several days later. The animal was again hydrated

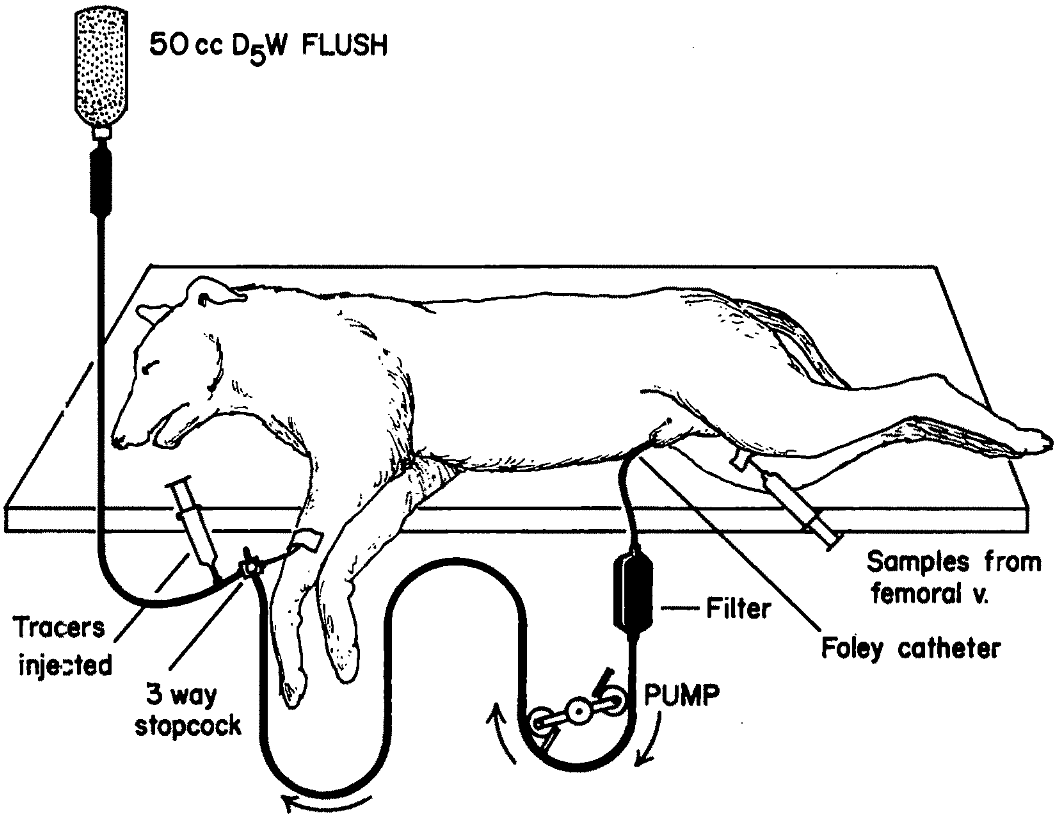

FIG. 1. The experimental design allowed for continuous sterile shunting of urine from the bladder into a forearm vein. By this method, the urinary excretion variable was eliminated.

the day prior to study and allowed only water that night. On the day of study the dog was given 10% of his body weight as Ringer's lactate solution intravenously over a one-hour period. Another hour was allowed to elapse for homeostasis. Baseline blood samples and hematocrits were obtained and the tracers injected. The experimental design was the same as that in the control study.

Determination of Fluid Volumes

Plasma volume (PV) was calculated by the extrapolation of the 10, 20, and 30 minute samples to zero time employing Evans blue dye plasma concentration.[14] From this value and the red cell hematocrit the red cell volume (RCV) and blood volume (BV) were determined.[16]

Thiocyanate quantitation of all blood samples was performed as described by Crandall and Anderson[8] and the values were plotted on semilog paper. The final dilution curve was then determined and the final equilibration exponential was plotted and extrapolated to zero time. This zero time value was then used to determine the thiocyanate extracellular fluid water (ECW_{SCN}) based on the principle of dilution where $C_1V_1 = C_2V_2$ or $V_2 = (C_1V_1/C_2)$. Tracer concentration and volume injected are indicated by C_1 and V_1 respectively, whereas C_2 and V_2 indicate the same parameters after fluid equilibration. No correction was made for metabolism, protein binding effect, or cellular uptake of thiocyanate during the five hours over which measurements were made.

Counts of ^{82}Br on aliquots of all plasma samples were made using standard counting techniques. Triplicate ^{82}Br standard dilutions were counted with the plasma samples. Sample counts/minute/ml were plotted on semilog paper against time and the final equilibration exponential was plotted and extrapolated to zero time as performed with thiocyanate. This value was used to calculate the uncorrected bromide (BrV). Using McMurrey's formula [$ECW_{Br} = (BrV - 0.6RCV - PV/1.11) + 0.92\ PV$] (23), the red cell uptake, plasma water and Donnan factor corrections were made. This *corrected* bromide extracellular water (ECW_{Br}) is the value used for comparison with thiocyanate space unless otherwise stated.

In addition to calculating extracellular fluid volumes for both ^{82}Br and SCN, exponential analysis for each curve was performed. All dilution curves were plotted on semilog paper and noted to follow three additive exponential paths. The first exponent represented intravascular mixing and occurred within the first few minutes of tracer injection. It was ignored in this study since interest was only toward diffusion, represented by the second exponential, and final extracellular fluid equilibration indicated by the third exponential. Since the dilution curve represented an additive phenomena, the second exponential plot was easily obtained by subtracting the extrapolated third equilibration exponential values from the dilution curve values. The determinations of the half time ($t_{1/2}$) of the second exponential offered an easy means for comparing diffusion time between control and overload situations. Others[4,29] have used this type of analysis to ascertain whether diffusion time for the extracellular fluid compartment was prolonged. Figs. 2–4 show the dilution curves and the $t_{1/2}$ of ^{82}Br and of SCN in a typical canine experiment.

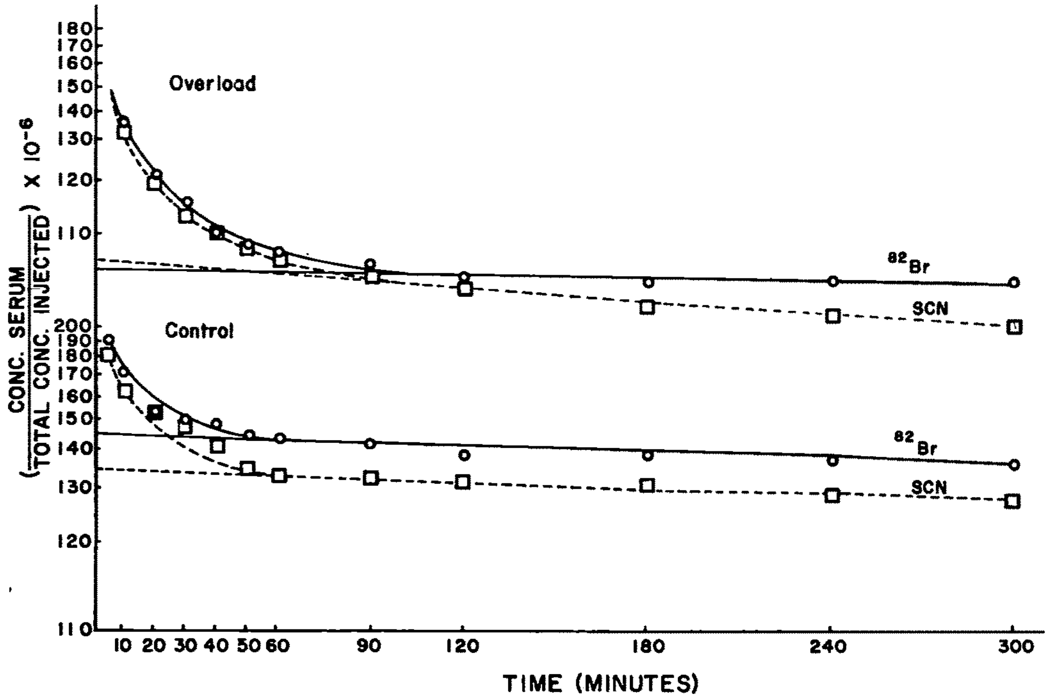

FIG. 2. ^{82}Br and SCN extracellular fluid volume dilution curves in dog #8. Extrapolation of the third, final exponential to zero time provided easy determination of the respective extracellular fluid volume. Note that more samples were obtained early in the curve where diffusion of ions was more rapid.

Total body water (TBW) as measured by deuterium oxide was determined by the microtechnique described by Turner, *et al.*[35]

All fluid compartment volumes were expressed as percentage of body weight for comparison purposes.

Patient Studies

All patients' studies were performed in a similar manner. The study was performed in the fasting patient over a period of 6 hours. Intravenous fluids were administered in minimal amounts during sampling to keep a large-bore external jugular catheter patent for obtaining blood samples. Tracer media were injected through a separate intravenous catheter in the arm and followed by 50 ml of 5% dextrose in water. Correction was made for the urinary excretion of ^{82}Br in calculating both the uncorrected (BrV) and the corrected volume (ECW_{Br}).

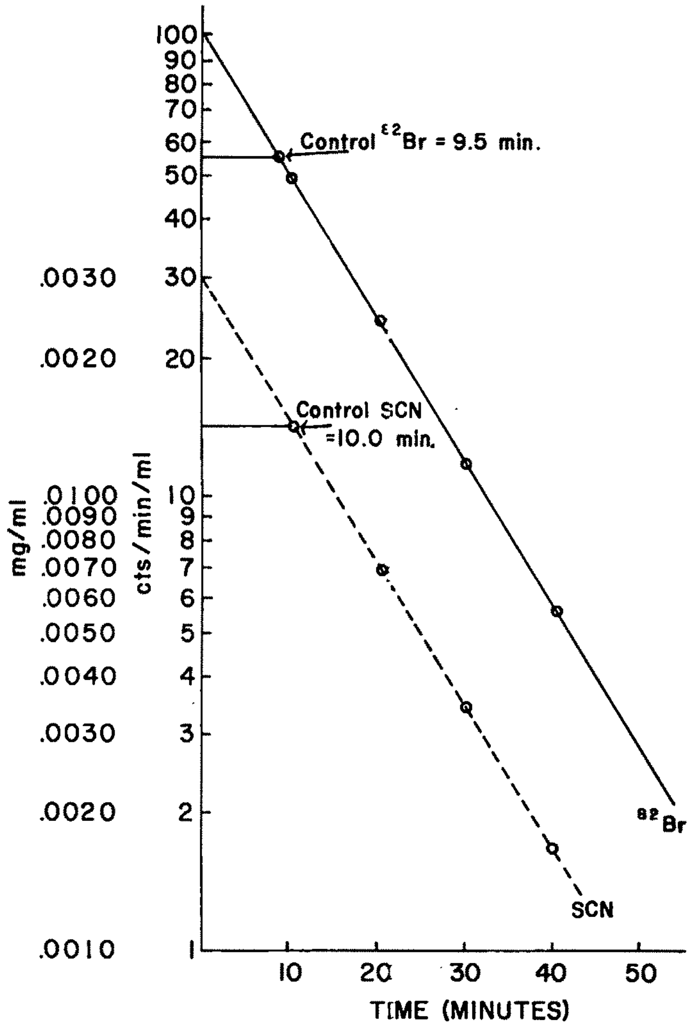

FIG. 3. ^{82}Br and SCN control second exponential half-times in dog #8. The second exponential plot was obtained by subtracting the extrapolated third and final exponential from the dilution curve. Diffusion times were 9.5 and 10.0 minutes for control Br $t_{1/2}$ and SCN $t_{1/2}$, respectively.

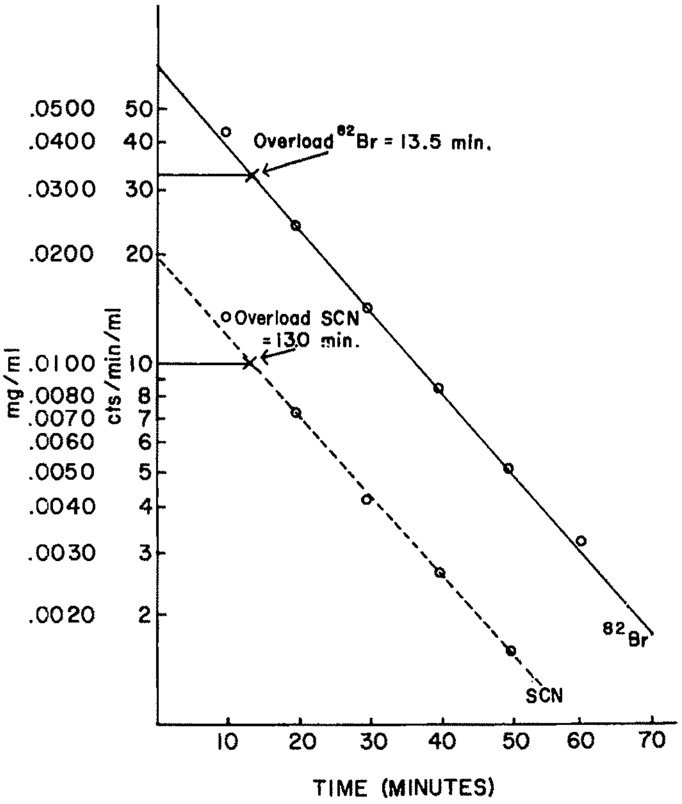

FIG. 4. ^{82}Br and SCN overload second exponential half-times in dog #8. Diffusion times are prolonged for both tracers as evidenced by longer $t_{1/2}$'s of 13.5 and 13.0 minutes respectively.

All volume measurements were based on preillness weight and were compared to predicted volumes by the regression equations of Moore, *et al.*[26] for TBW, BV, RCV, PV, and ECW_{Br}. The work by Lavietes, *et al.*,[21] Stewart and Rourke,[34] and Crandall and Anderson[8] formed the basis of comparison for ECW_{SCN}.

Results

Experimental Canine Data

Each animal was studied in control and overload conditions and the results are tabulated in Tables 1 and 2. The mean control extracellular water as determined by ^{82}Br (ECW_{Br}) was 28.5 ± 1.5% (standard deviation) of body weight, whereas the mean thiocyanate volume (ECW_{SCN}) was 35.0 ± 2.1%. The mean control total body water was 71.2 ± 7.1% of the body weight.

Analysis of the dilution curves for both extracellular

TABLE 1. *Mean Control Fluid Compartments (10 Dogs)*

	Percentage of Body Weight ± S.D.
BrV (uncorrected)	33.6 ± 1.6%
ECW_{Br}(corrected)*	28.5 ± 1.5%
ECW_{SCN}	35.0 ± 2.1%
TBW	71.2 ± 7.1%

* McMurrey formula, McMurrey, *et al.*[23]

TABLE 2. *Mean Overload Fluid Compartments (10 Dogs)*

	Percentage of Body Weight ± S.D.
BrV (uncorrected)	44.0 ± 2.6
ECW_{Br} (corrected)*	38.0 ± 2.5
ECW_{SCN}	45.6 ± 3.8
TBW	79.8 ± 6.1

* McMurrey formula, McMurrey, *et al.*[23]

tracer substances in control animals indicates that they can be described by 3 additive single exponential rates. Ignoring the first exponential, representing mixing, attention in this study was directed toward the second exponential component of the dilution curve, representing diffusion, which exhibited a mean $t_{1/2}$ of 9.9 ± 1.7 minutes for ^{82}Br and 9.8 ± 1.7 minutes for SCN (Table 3).

In the overload experiments (fluid administered, 10% of the body weight), mean extracellular water volumes were 38.0 ± 2.5% of the body weight for ^{82}Br (ECW_{Br}) and 45.6 ± 3.8% of the body weight for thiocyanate (ECW_{SCN}). The mean total body water in the overload animals was 79.8 ± 6.1%.

Again, analysis of the dilutional curves revealed three exponential components. The second, representing diffusion gave a mean $t_{1/2}$ of 12.3 ± 1.7 minutes for ^{82}Br and 10.2 ± 3.0 minutes for SCN.

Clinical Results

Eleven patients who had fluid composition studies for reasons other than fluid overload, and were felt to be under homeostatic fluid conditions, were used to determine normal diffusion rates by measuring the second exponential equilibration half times ($t_{1/2}$) for ^{82}Br and SCN. These were calculated to be 15.2 ± 3.0 minutes for ^{82}Br and 16.3 ± 4.7 minutes for SCN and form the basis of predicted values in Table 4.

Case Reports

Case 1. *Overload after Cardiopulmonary Bypass.* V. H. (#222991) was a 32-year-old female diagnosed to have mitral regurgitation secondary to rheumatic valvular disease. This had previously been documented with cardiac catheterization. When the preoperative fluid composition studies were performed, the patient's weight was 148 pounds (67.3 kg). Within 24 hours after cardiopulmonary bypass for mitral valve prosthetic replacement, the fluid composition studies were repeated. Her weight had increased to 161.5 pounds (73.4 kg), an increase of about 6 kg. Her clinical appearance suggested overload with chemosis and periorbital edema.

TABLE 3. *Mean Half Life ($t_{1/2}$) of Second Exponential in Dilution*

	Curve (10 Dogs) *Minutes ± S.D.*
Control	
Br $t_{1/2}$	9.9 ± 1.7
SCN $t_{1/2}$	9.8 ± 1.7
Overload	
Br $t_{1/2}$	12.3 ± 1.7
SCN $t_{1/2}$	10.2 ± 3.0

Table 4 shows that blood volume was elevated both preoperatively and postoperatively, compared to predicted values. Extracellular water for both SCN and ^{82}Br was above normal postoperatively, suggesting fluid overload. Since total body water was low in both measurements, intracellular fluid volume must have been relatively decreased. It is important in this particular case to know that the patient had been taking diuretics and digitalis preoperatively. Of particular interest is the prolonged diffusion time for both tracers postoperatively as manifested by the increased $t_{1/2}$, greater for ^{82}Br than for SCN. In fact, postoperatively an additional exponential appeared early in the curve for ^{82}Br with a $t_{1/2}$ of 6 minutes. This phenomenon was implied in the SCN curve but there were too few points to plot it.

Case 2. *Phlegmasia Alba Dolens.* M. L. (#237385), a 22-year-old male, was shot in the abdomen sustaining a hole in the left external iliac vein which required 30 units of whole blood during surgery until bleeding could be controlled with complete ligation of the vessel; in addition, there were multiple perforations of the small bowel. On the fourth postoperative day, he exhibited circumferential edema of his left leg from the groin to the toes. At this time fluid compartment studies were obtained. His weight was 127.3 kg compared to a pre-illness estimate by the patient of 240 pounds (109.1 kg).

Total body water, as expected, was above normal. The ECW_{Br} and ECW_{SCN} were both elevated. Most impressive in this patient was the vastly prolonged $t_{1/2}$ of 27 minutes for both tracers. In this patient, the prolonged $t_{1/2}$ was the most reliable evidence of overload, although both ECW_{Br} and ECW_{SCN} demonstrated this condition.

Case 3. *Ascites.* S. S. (#234527) was a 52-year-old male admitted because of respiratory distress secondary to ascites from post-hepatitic cirrhosis. Before development of ascites, several months prior to admission, he weighed 240 pounds (109.1 kg). At the time of study he weighed 123.5 kg. Physical examination confirmed obvious fluid overload with ascites and 4+ pitting presacral, extremity, and scrotal edema.

Both ^{82}Br and SCN tracers indicated an increased extracellular fluid volume when compared to predicted values based upon the pre-illness weight. Both the predicted TBW and the measured TBW, when calculated with the expanded extracellular fluid volume, indicated an intracellular dehydration. The ^{82}Br $t_{1/2}$ was greater than the SCN $t_{1/2}$, suggesting that SCN diffuses more readily into this particular "compartment" of extracellular fluid volume.

Case 4. *Nephrotic Syndrome.* E. S. (#201755) was a 29-year-old male with a complicated history of approximately 18 months' duration, beginning with bilateral lower extremity thrombophlebitis and pulmonary embolus treated adequately with anticoagulation. Lower extremity edema continued, however, and eventually severe renal disease became manifest with severe proteinuria (25 gms protein/day) and anasarca. This was controlled fairly well with medications. A right above-the-knee amputation had been performed 3 months prior to referral because of combined venous stasis and arterial insufficiency. Upon admission to this hospital for similar problems in his left leg, the patient was noted to have anasarca to the nipples, a cold, swollen left leg, and no femoral pulse. Immediately after admission the patient had fluid composition studies; his weight at this time was 64.2 kg. After intensive medical management with diuretics, prior to left A/K amputation, his weight declined to 56.8 kg.

TABLE 4. *Patient Studies*

Case	Weight (Kg)	BV*	ECW_{Br}*	ECW_{SCN}*	TBW*	$t_{1/2}$Br†	$t_{1/2}$SCN†
#1, V.H.							
Preop	67.3	8.6	20.6	24.1	47.8	17.0	21.0
Postop		7.3	22.8	28.7	54.4	26.0	22.5
Predicted		5.9	21.2	—	56.1	15.2 ± 3.0	16.3 ± 4.7
#2, M.L.							
Measured	109.1	5.2	25.4	32.4	62.3	27.0	27.0
Predicted		5.4	20.2	—	52.6	15.2 ± 3.0	16.3 ± 4.7
#3, S.S.							
Measured	109.1	7.2	36.1	36.1	52.5	35.0	19.0
Predicted		5.4	20.2	—	49.8	15.2 ± 3.0	16.3 ± 4.7
#4, E.S.							
Measured	56.8	7.6	36.5	41.9	67.2	12.0	11.0
Predicted		7.9	26.4	—	63.7	15.2 ± 3.0	16.3 ± 4.7
#5, M.F.							
Measured	57.3	5.3	29.4	34.7	61.1	25.0	25.0
Predicted		6.2	22.6	—	48.5	15.2 ± 3.0	16.3 ± 4.7

* Percentage of body weight
† Minutes

The measured blood volume in this patient was normal. The total body water likewise was determined to be normal. Both ^{82}Br and SCN measurements of extracellular fluid volume were elevated when compared to predicted values for that weight. The clinical evidence of extracellular fluid overload was thus confirmed. In view of a normal TBW, there was a low intracellular fluid volume suggestive of severe wasting and probably a small lean body mass. Interestingly, the ^{82}Br $t_{1/2}$ and SCN $t_{1/2}$ were within the normal range, whereas one would have expected them to be prolonged in fluid overload.

Case 5. *Retroperitoneal Hematoma.* M. F. (#121464) was a 44-year-old female admitted shortly after being struck by an automobile. She was in profound shock, secondary to bilateral acetabular fractures, upon arrival at the emergency room. This responded initially to crystalloid and colloid solutions. Over the next 24 hours the patient required 4000 cc of whole blood in addition to further crystalloid and colloid fluids to prevent recurrent shock. An IVP showing grossly deviated ureters confirmed a large retroperitoneal hematoma. A physical examination substantiated this with findings of a large flank ecchymoses. At 72 hours, fluid studies were performed after the patient had gained 8 kg (57.3 kg pre-accident and 65 kg on day of study).

The blood volume at the time of study was lower than that predicted on the basis of pre-illness weight. Both the extracellular fluid volume and the $t_{1/2}$ were increased for ^{82}Br and for SCN. Total body water was also higher than the predicted value. The large retroperitoneal fluid collection was obviously the source of these enlarged compartments and prolonged $t_{1/2}$.

Discussion

Animal Experiments

In animals 1, 2, and 3, control fluid compartment data were obtained twice with 8 to 10-days interval between determinations (Table 5). The maximal difference for corrected bromide (ECW_{Br}), uncorrected bromide (BrV), and thiocyanate (ECW_{SCN}) extracellular fluid volumes in these three animals was 2.1% of the body weight, indicating good reproducibility.

Likewise, comparisons between the control and the overload extracellular fluid volumes showed 98.4 ± 4.0% of the administered fluid was accounted for by ^{82}Br and 102.6 ± 7.5% by SCN. This suggested that both ions were reliable for these measurements, but that ^{82}Br was slightly more precise than SCN. Most of this fluid remained extracellular, as demonstrated by these high percentages. Consistent intracellular fluid volumes in both control and overload measurements gave additional evidence that most, if not all, the administered fluid remains extracellular. The ^{82}Br values were 42.7% and 41.8% of the body weight for control and overload calculated intracellular water volumes respectively, whereas SCN values were 36.2 and 34.2% of the body weight respectively.

In comparing the extracellular fluid volume measured by ^{82}Br to that measured by SCN, an interesting question arose; namely, which correlated better, the uncorrected bromide volume (BrV) and thiocyanate (ECW_{SCN}), or the corrected bromide volumes (ECW_{Br}) and thiocyanate volume (ECW_{SCN})? Careful study of the data revealed that uncorrected bromide (BrV) and thiocyanate (ECW_{SCN}) measurements of extracellular fluid were

TABLE 5. *Comparison of Control Fluid Compartment Determinations* (Dogs)*

Dog#	Br Volume (Uncorrected) I	Br Volume (Uncorrected) II	ECW_{Br} (Corrected) I	ECW_{Br} (Corrected) II	ECW_{SCN} I	ECW_{SCN} II
1	34.2	36.3	29.1	31.2	38.5	39.1
2	35.1	34.2	30.2	29.2	36.0	35.1
3	35.1	37.2	29.3	31.2	36.0	37.9

* Percentage of body weight

closer in both control and overload conditions (coefficient correlation = 0.948) than measurements of corrected bromide (ECW_{Br}) and thiocyanate (ECW_{SCN}) extracellular fluid (coefficient correlation = 0.889). The linear correlation graph in Fig. 5 demonstrates this proportionate compartment measurement when comparing ^{82}Br and SCN. Perhaps calculation of red cell uptake, the Donnan effect, and other undetermined variables for SCN might result in lower percentages which would approximate the corrected bromide values. McMurrey's[23] formula makes adjustments for these variables when using ^{82}Br as the tracer.

During our investgiations, we confirmed McMurrey's ratio for RBC uptake of ^{82}Br by a more direct method, using Evans blue dye to measure the amount of trapped plasma in packed red cells rather than by estimation based on centrifugal force and time. In 4 *in vitro* experiments the ratio of 1 ml of RBC^{82}Br to 1 ml of plasma ^{82}Br averaged 0.62 at one hour and 0.61 at 5 hours.

Prolongation of diffusion by an increased half-time ($t_{1/2}$) of the second exponential of the dilution curves in the overload animal was expected. This is a logical supposition, since more fluid in the overload condition contributes to a larger compartment and therefore more equilibration time requirement for ^{82}Br or SCN to move from intravascular locations to interstitial areas. Indeed, this does occur when using ^{82}Br as the tracer as has been shown by a mean half-time of 9.9 ± 1.7 minutes for the control group and 12.3 ± 1.7 minutes for the overload studies (Table 3). This difference was statistically significant ($P \leq 0.01$). However, comparison of the SCN mean half-time values of 9.8 ± 1.7 minutes and 10.2 ± 3.0 for control and overload groups, respectively, showed no significant difference ($P \leq 0.50$). This interesting finding could not readily be explained unless an undetermined error was made in the SCN $t_{1/2}$ calculations of three animals in which ^{82}Br $t_{1/2}$ but not SCN $t_{1/2}$ increased following overload. Omission of these three animals resulted in a significantly prolonged SCN $t_{1/2}$ ($P \leq 0.01$).

Patient Studies

Our experimental observations were confirmed clinically. Corrected ^{82}Br extracellular fluid volumes (ECW_{Br}) were greater in all 5 patients than the predicted normal values for their weights according to regression equations by Moore.[26] Regression for thiocyanate equations based on body weight could be calculated from Crandall and Anderson's[8] work and from that of Steward and Rourke,[34] but correlation coefficients for both were too

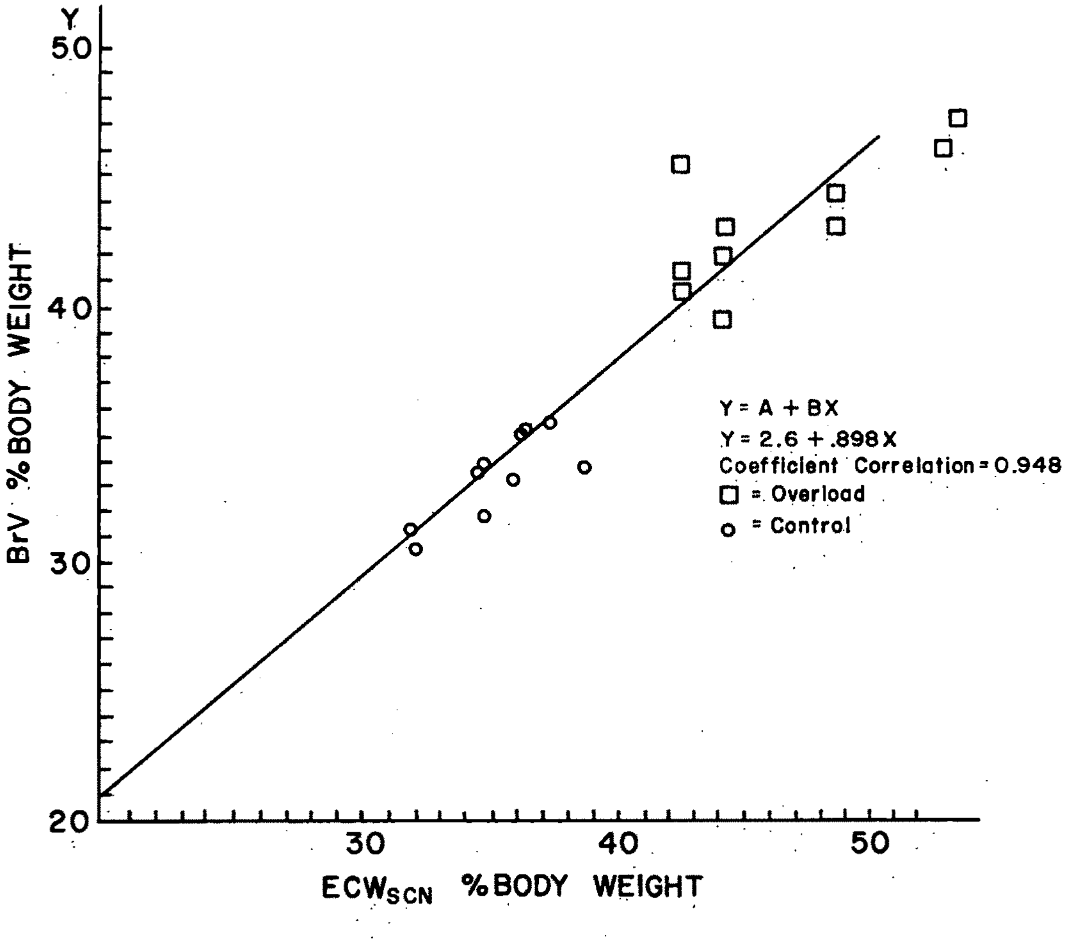

FIG. 5. Correlation of uncorrected bromide (BrV) and thiocyanate (ECW_{SCN}) compartments in dogs. The high correlation coefficient demonstrates the proportionate measurements of these 2 tracer substances.

low to allow reliable interpretation of normal thiocyanate volumes. However, compared to average normal values, for that body weight based on the above works, the extracellular thiocyanate volume (ECW_{SCN}) was increased in all 5 of our patients. Values showing expanded extracellular fluid compartments measured under similar selected clinical conditions using a variety of tracers agree closely with these findings.[2,3,7,8,15,21,22,29]

The second exponential diffusion times for thiocyanate and radioactive bromide were more variable under clinical situations. Normal half-times as measured in 11 patients under homeostatic fluid conditions were 15.2 ± 3.0 minutes for ^{82}Br and 16.3 ± 4.7 minutes for SCN. The ^{82}Br $t_{1/2}$ agrees closely with results of Pluth.[29] Thus, in patients 1, 2 and 5 both ^{82}Br and SCN $t_{1/2}$ were increased, correlating well with the experimental finding of prolonged equilibration under overload conditions. The additional exponential in Case 1 (overload after cardiopulmonary bypass) has been reported by other investigators.[4] The ^{82}Br equilibration was prolonged in patient 3 but SCN was not, suggesting easier diffusion into ascitic fluid of the thiocyanate ion, an observation we cannot explain. Patient 4, although clinically overloaded with fluid, had normal $t_{1/2}$'s for the second exponential.

Summary and Conclusions

Body fluids were measured in 10 dogs under normal and fluid overload conditions, with emphasis upon comparison of thiocyanate and radioactive bromide determinations of extracellular fluid space. A high degree of correlation was noted when comparing thiocyanate (ECW_{SCN}) and uncorrected bromide (BrV) (correlation coefficient 0.948) as well as thiocyanate (ECW_{SCN}) and corrected bromide (ECW_{Br}) by McMurrey's formula (correlation coefficient 0.889). Comparisons of both tracers between control and overload extracellular fluid volumes showed most the administered fluid to remain extracellular, as 98.4 ± 4.0% was accounted for by ^{82}Br and 102.6 ± 7.5% by SCN. In addition, there was demonstrated a prolongation of diffusion in the overload animals for ^{82}Br in contrast to the SCN where there was no significant difference between control and overload studies.

Fluid composition measurements were also made in 5 selected patients under fluid overload situations. Extracellular fluid volumes were greater in all 5 patients using ^{82}Br and SCN tracers. Final equilibrium, resulting from prolonged diffusion, was delayed in 3 patients for both tracers.

In conclusion, this study has demonstrated that both ^{82}Br and SCN are reliable and highly comparable tracer substances in documenting expanded extracellular fluid compartments in overload experiments and clinical situations of fluid overload. It has been shown that final equilibration is prolonged under fluid overload conditions experimentally. Selected clinical situations create more variability in prolongation of final equilibration. Nevertheless, expanded extracellular fluid compartment size and prolonged equilibration using either ^{82}Br or SCN are valuable clues to fluid overload conditions.

Acknowledgments

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References

1. Berson, S. A. and Yalow, R. S.: Critique of Extracellular Space Measure With Small Ions; Na^{24}, and Br^{82} Spaces. Science, **121**:34, 1955.
2. Blumberg, A., Help, W. B., Hegstron, R. M. and Scribner, B. H.: Extracellular Volume in Patients with Chronic Renal Disease Treated for Hypertension by Sodium Restriction. Lancet, **2**:69, 1967.
3. Breckenridge, I. M., Digerness, S. B. and Kirklin, J. W.: Increased Extracellular Fluid After Open Intracardiac Operation. Surg. Gynec. Obstet., **131**:53, 1970.
4. Breckenridge, I. M., Digerness, S. B. and Kirklin, J. W.: Distribution Volume, Equilibration Time, and Exponential Analysis of ^{82}Br After Open Intracardiac Operations. Ann. Surg., **171**:583, 1970.
5. Brodie, B. B., Brand, E. and Leshin, S.: The Use of Bromide as a Measure of Extracellular Fluid. J. Biol. Chem., **130**:555, 1939.
6. Cardozo, R. H. and Edelman, I. S.: The Volume of Distribution of Sodium Thiosulfate as a Measure of the Extracellular Fluid Space. J. Clin. Invest., **31**:280, 1952.
7. Cleland, J., Pluth, J. R., Tause, W. M. and Kirklin, J. W.: Blood Volume and Body Fluid Compartment Changes Soon After Closed and Open Intracardiac Surgery. J. Thorac. Cardiovasc. Surg., **52**:698, 1966.
8. Crandall, L. A. and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate. Amer. J. Dig. Dis. Nutr., **1**:126, 1934.
9. DeBoer, A.: Body Fluid Compartment Changes Following Large Volume Hemodilution. Arch. Surg., **98**:602, 1969.
10. Gamble, J. L., Jr. and Robertson, J. S.: Volume of Distribution of Radioactive Chloride in Dogs: Comparisons with Sodium, Bromide, and Inulin Spaces. Amer. J. Physiol., **171**:659, 1952.
11. Gamble, J. L., Robertson, J. S., Hannigan, C. A., Foster, C. G. and Farr, L. E.: Chloride, Bromide, and Sodium, and Sucrose Spaces in Man. J. Clin. Invest., **32**:483, 1953.
12. Gaudino, M., and Levitt, M. F.: Inulin Spaces as a Measure of Extracellular Fluid, Amer. J. Physiol., **157**:387, 1949.
13. Gaudino, M., Schwartz, I. L. and Levitt, M. F.: Inulin Volume of Distribution as a Measure of Extracellular Fluid in Dog and Man. Proc. Soc. Exp. Biol. Med., **68**:507, 1948.
14. Gibson, J. G., II and Evans, W. A.: Clinical Studies of the Blood Volume: Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectophotometer. J. Clin. Invest., **16**:301, 1937.
15. Gilligan, D. R. and Altschule, M. D.: The Rate of Attainment of Diffusion Equilibrium for Thiocyanate Between Plasma and Transudates Following the Intravenous Injection of Sodium Thiocyanate in Patients with Edema. J. Clin. Invest., **18**:501, 1939.
16. Guyton, A. C.: Textbook of Medical Physiology. Philadelphia, W. B. Saunders, 443, 1961.
17. Hastings, A. B., and VanDyke, H. B.: Studies of Bromide

Distribution in the Blood. *In Vitro* Experiments of Bromide and Chloride Distribution. J. Biol. Chem., **92**:13, 1931.

18. Hastings, H. B. and VanDyke, H. B.: Studies of Bromide Distribution in the Blood. The Distribution of Bromides and Chlorides in the Blood of Dogs Following Oral Administration of Sodium Bromide. J. Biol. Chem., 92:27, 1931.
19. Howe, C. T. and Ekins, R. P.: The Bromide Space After the Intravenous Administration of ^{82}Br. J. Nucl. Med., 4:469, 1962.
20. Kaltreider, N. L., Meneely, G. R., Allen, J. R. and Bale, W. F.: Determination of the Volume of the Extracellular Fluid of the Body with Radioactive Sodium. J. Exp. Med., **74**:569, 1941.
21. Lavietes, P. H., Bourdillon, J. and Klinghoffer, K. A.: The Volume of Extracellular Fluids of the Body. J. Clin. Invest., **15**:261, 1936.
22. Madison, L. L., Teng, H. C., Seldin, D. W., Reid, A. F. and MacDonald, R.: Radiosulfate as a Measure of Extracellular Volume in Edematous States. Clin. Res. Proc., 3:126, 1955.
23. McMurrey, J. D., Boling, E. W., Davis, J. M., Parker, H. V., Magnus, I. C., Ball, M. R. and Moore, F. D.: Body Composition: Simultaneous Determination of Several Aspects by the Dilution Principle. Metabolism, **7**:651, 1958.
24. Moore, F. D., Hartsuck, J. M., Zollinger, R. M. and Johnson, J. E.: Reference Models for Clinical Studies by Isotope Dilution. Ann. Surg., **168**:671, 1968.
25. Moore, F. D., Muldowney, F. P., Haxhe, J. J., Marczynska, A. W., Ball, M. R. and Boyden, C. M.: Body Composition in the Dog. Findings in the Normal Animal. J. Surg. Res., **2**:245, 1962.
26. Moore, F. D., Olesen, K. H., McMurrey, J. D., Parker, H. V., Ball, M. R., and Boyden, C. M.: The Body Cell Mass and Its Supporting Environment: Body Composition in Health and Disease. Philadelphia, W. B. Saunders, 1963.
27. Overman, R. R.: Permeability Alterations in Disease. J. Lab. Clin. Med., **31**:1170, 1946.
28. Pluth, J. R., Cleland, J., Tauxe, W. N. and Kirklin, J. W.: Late Changes in Body Fluid and Blood Volume After Intracardiac Surgery. J. Thorac. Cardiov. Surg., **56**:108, 1968.
29. Pluth, J. R., Cleland, J., Meador, C. K., Tauxe, W. N., Kirklin, J. W. and Moore, F. D.: Effect of Surgery on the Volume Distribution of Extracellular Fluid Determined by the Sulfate and Bromide Methods. Symposium on Compartments, Pools, and Spaces in Medical Physiology. U. S. Atomic Energy Commission, p. 217, 1967.
30. Reid, D. J., Digerness, S. and Kirklin, J. W.: Intracellular Fluid Volume in Surgical Patients Measured by the Simultaneous Determination of Total Body Water and Extracellular Fluid. Surg. Forum, **18**:29, 1967.
31. Ryan, R. J., Pascal, L. R., Inoye, T. and Bernstein, L.: Experiences with Radiosulfate in the Estimation of Physiologic Extracellular Water in Healthy and Abnormal Man. J. Clin. Invest., **35**:1119, 1956.
32. Shires, T., Williams, J. and Brown, F.: Simultaneous Measurement of Plasma Volume, Extracellular Fluid Volume, and Red Blood Cell Mass in Man Utilizing I^{131}, S^{35}O$_4$, and Cr^{51}. J. Lab. Clin. Med., **55**:776, 1960.
33. Smith, P. K., Eisenman, A. J. and Winkler, A. W.: The Permeability of Human Erythrocytes to Radioactive Chloride and to Bromide and Iodide. J. Biol. Chem., **141**: 555, 1941.
34. Stewart, J. D. and Rourke, G. M.: On the Measurement of Extracellular Fluid Volume with Thiocyanate and Body Fluid Analysis in 33 Normal Individuals. J. Lab. Clin. Med., **26**:1383, 1940.
35. Turner, M. D., Neely, W. A., Adcock, R. and Turner, A. C.: A Micromethod for the Determination of Deuterium Oxide in Biological Fluids. Microchem. J., 8:395, 1964.
36. Wallace, G. B. and Brodie, B. B.: The Distribution of Administered Bromide in Comparison with Chloride and Its Relation to Body Fluids. J. Pharmacol. Exp. Ther., **65**:214, 1939.
37. Wallace, G. B. and Brodie, B. B.: The Passage of Bromide, Iodide, and Thiocyanate Into and Out of the Cerebrospinal Fluid. J. Pharmacol. Exp. Ther., **68**:50, 1940.
38. Walser, M., Seldin, D. W. and Grollman, A.: An Evaluation of Radiosulfate for the Determination of the Volume of Extracellular Fluid in Man and Dogs. J. Clin. Invest., **32**: 299, 1953.
39. Weir, E. G.: Determination of the Total Chloride Content of Animals Following Administration of Sodium Bromide. Am. J. Physiol., **127**:338, 1939.
40. Weir, E. G. and Hastings, A. B.: The Distribution of Bromide and Chloride in Tissues and Body Fluids. J. Biol. Chem., **129**:547, 1939.
41. Winkler, A. W., Elkinton, J. R. and Eisenman, A. J.: Comparison of Sulfocyanate With Radioactive Chloride and Sodium in the Measurement of Extracellular Fluid. Amer. J. Physiol., **139**:239, 1943.

Portal-Systemic Shunt in Hepatic Cirrhosis:

Does the Type of Shunt Decisively Influence the Clinical Result?

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PORTAL-SYSTEMIC SHUNT has for many years been the treatment of choice for portal hypertension secondary to hepatic cirrhosis. That the form most frequently used, direct portacaval anastomosis, is effective in preventing rebleeding from esophagogastric varices is well established, but whether it significantly prolongs survival is open to question.[7,13,14] The undoubted benefit of protection from variceal bleeding may be outmatched by a high postoperative mortality rate, a high incidence of encephalopathy, and a high mortality rate from hepatocellular failure. The consensus at present is to ascribe these disadvantages to reduction of total blood flow through the liver as a result of diversion of portal venous blood into the vena cava.[21] Surgeons have in consequence investigated the hemodynamic effects of alternative methods of portal diversion, with a view to devising procedures which will cause minimal reduction of hepatic blood flow and, therefore, minimal deterioration of hepatic function.

Previous work, conducted in experimental animals,[3] suggested that partial, as opposed to total, portal-systemic shunt might lower portal pressure enough to preclude the risk of gastrointestinal hemorrhage while leaving it high enough to ensure adequate hepatic blood flow. To achieve this in human subjects there are 2 essential prerequisites: 1) continuity of the portal trunk must be maintained, at least in part, so that the liver still receives some portal blood; and 2) the anastomotic stoma must be of small caliber. The techniques which, *a priori,* seemed most likely to fulfil these requirements were 1) side-to-side portacaval anastomosis using a small stoma, a procedure first proposed by Bismuth *et al.*[4] in 1966 and which is the simplest and the most direct type of partial portal-systemic shunt, and 2) spleno-renal anastomosis, in which the continuity of the portal trunk remains intact and the volume flow through the shunt is limited by the caliber and the length of the splenic vein.[8] Within this context, we have studied 3 different shunt techniques. Analysis of the results has led us to doubt whether hemodynamic status is in fact the cardinal element in determining the future of patients who have undergone shunting operations.

Patients and Methods

In the years 1965 through 1972 elective portal-systemic shunts were performed in 120 patients, 83 men and 37 women, with portal hypertension resulting from intrahepatic block due to cirrhosis (Table 1). Three types of shunt procedure were used: total direct portal-systemic shunt by end-to-side, or large-stoma side-to-side, portacaval anastomosis in 25 patients; partial direct portal-systemic shunt by small-stoma side-to-side portacaval anastomosis in 23 patients; and central splenorenal anastomosis in 72 patients. Patients were randomly assigned to the different operative groups.

The mean age of the patients was 50 ± 11 (mean ± SD) years. The youngest patient was aged 21 years and

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TABLE 1. *120 Patients with Hepatic Cirrhosis Submitted to Portal-Systemic Shunt*

Type of Shunt	Number of Patients	Men	Women	Mean Age (Years)	Good Risk*	Poor Risk*	Cirrhosis Alcoholic		Nature of Operation	
							Yes	No	Therapeutic	Prophylactic
Total portacaval	25	21 (84)	4 (16)	53 ± 9	15 (60)	10 (40)	23 (92)	2 (8)	25 (100)	0
Partial portacaval	23	15 (65.3)	8 (34.7)	48 ± 9	13 (57.6)	10 (43.4)	20 (86.9)	3 (13.1)	23 (100)	0
Splenorenal	72	47 (65.3)	25 (34.7)	49 ± 12	41 (57)	31 (43)	32 (44.4)	40 (55.6)	68 (94.5)	4 (5.5)
Totals	120	83 (69.2)	37 (30.8)	50 ± 11	69 (57.5)	51 (42.5)	75 (62.5)	45 (37.5)	116** (96.6)	4 (3.4)

Figures in brackets are percentages.

* For definition see Table 3.

** For gastrointestinal hemorrhage in 115 patients; for ascites in one patient.

the oldest 74 years; 55% of the patients were aged over 50 years. Age distribution was approximately the same in the three operative groups.

The causes of cirrhosis are listed in Table 2. Alcoholic cirrhosis was the best represented form, being present in 75 (62.5%) of the 120 patients.

All the patients had esophagogastric varices as demonstrated by barium swallow and/or esophagogastroscopy. Two patients also had peptic ulcers. In 4 patients who had associated portal thrombosis revealed by angiography, the thrombus was removed at the time of shunting. The presence of hepatoma was routinely excluded. In 115 patients the indication for portal-systemic shunt was a history of bleeding from esophagogastric varices. We considered only subjects who had portal-systemic shunt as an elective procedure, performed at least 6 weeks after a bleeding episode. The patients were divided into "good-risk" and "poor-risk" categories (Table 3) according to a modification of the criteria proposed by Hermann *et al.*[12]

All the operations were performed under anesthesia with sodium gammahydroxybutyrate (Egic, 45-Amilly, France) and by an abdominal approach. Pressure in the portal vein and in the inferior vena cava, or in the splenic and renal veins, was measured before and after anastomosis. Special care was taken to keep blood loss to a minimum. During the last two years Australia-antigen-negative fresh blood only has been used.

Total portal-systemic shunt was effected either by end-to-side portacaval anastomosis (12 patients) or by large-stoma side-to-side portacaval anastomosis with a minimal stomal length of 20 mm and a portal-caval pressure gradient of about 3 mm Hg (13 patients). In small-stoma side-to-side portacaval anastomosis the maximal length of the stoma was 15 mm and the portal-caval pressure gradient was approximately 7 mm Hg. Splenorenal shunt was done by a modification of the technique introduced by Clatworthy and Boles in children.[8] In order to use as short a length of splenic vein as possible we cut the thick pad of lymphocellular tissue which in many adult cirrhotics lies to the left of the superior mesenteric artery and which may constitute an obstacle to bringing the splenic and renal veins together.

After operation, assessment of hepatic and cerebral function and roentgenographic investigation of the esophagogastric varices were performed routinely in each patient before discharge from the hospital. Angiographic visualization of the anastomosis was performed in 11 patients either by means of a catheter left in the umbilical vein, or by selective superior mesenteric angiography. Instructions were given to refrain from alcohol and from certain drugs, in particular drugs containing acetylsalicylic acid. Follow-up examinations were conducted at intervals of 2 months, 6 months, and one year after operation and thereafter annually. All the patients, except one of whom trace was lost, had been seen within 6 months of preparation of this paper in August 1972.

TABLE 2. *Causes of Hepatic Cirrhosis in 120 Patients Submitted to Portal-Systemic Shunt*

Type of Shunt	Type of cirrhosis					Number of Patients
		Non-alcoholic				
	Alcoholic	Postnecrotic	Primary Biliary	Hemochromatosis	Unknown	
Total portacaval	23	0	0	0	2	25
Partial portacaval	20	0	0	0	3	23
Splenorenal	32	7	2	2	29	72
Total	75	7	2	2	34	120

TABLE 3. *120 Patients with Hepatic Cirrhosis Submitted to Portal-Systemic Shunt. Criteria for Grouping in Relation to Surgical Risk*

Criteria	Good-risk	Poor-risk
Previous episodes of hepatocellular failure	0	+
Nutritional status	Good	Poor
Encephalopathy	0	+
Ascites	0 or under control	+
Serum albumin (g per 100 ml)	>3.0	<3.0
Serum bilirubin (mg per 100 ml)	<2.0	>2.0
Prothrombin time (% of normal)	>40	<40

Modified from Hermann *et al.*[15]

Results

Intraoperative Hemodynamics (Fig. 1). Of the 3 portal-systemic shunt procedures used, total direct portacaval anastomosis produced the greatest fall in portal pressure (14.6 mm Hg), the lowest post-shunt portal pressure (11.5 mm Hg), and a post-shunt portal-caval pressure gradient of 3.4 ± 3.1 (mean ± SD) mm Hg. Partial direct portacaval anastomosis lowered the portal pressure by only 9.6 mm Hg to 14.4 mm Hg, and maintained the highest portal-caval pressure gradient, namely, 7.2 ± 2.6 (mean ± SD) mm Hg. The difference between the portal-caval gradients after total and partial portacaval anastomosis respectively is significant (P < 0.01) (Fig. 2). Whereas splenorenal anastomosis gave a post-shunt splenic vein pressure of 15.1 mm Hg, that is, in the same order of values as portal vein pressure after partial direct portacaval anastomosis, it left a splenorenal pressure gradient of only 1.8 mm Hg.

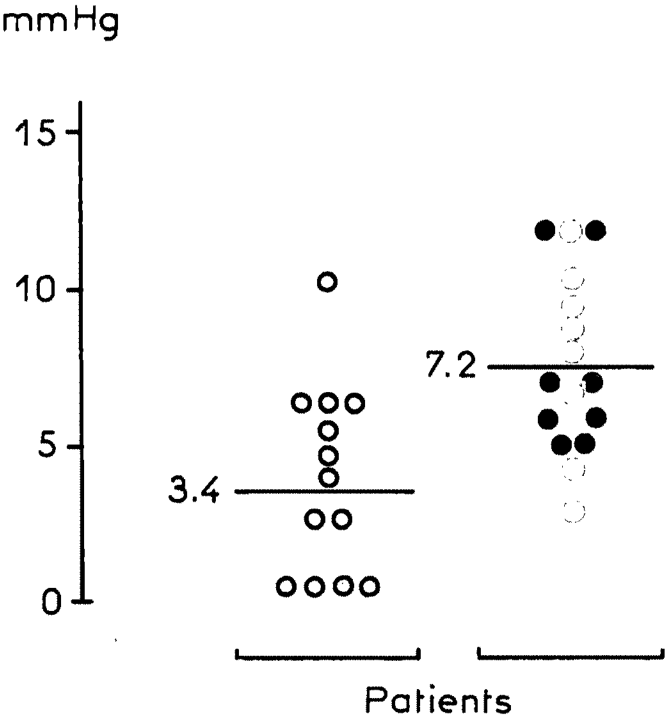

FIG. 2. Portal vein-inferior vena cava pressure gradients in 13 patients who had total direct portacaval anastomosis ○ and 17 patients who had partial direct portacaval anastomosis ● ($P < 0.01$).

Postoperative Angiography. After small-stoma side-to-side portacaval anastomosis diversion of portal blood was partial in all the cases studied; this is well illustrated in Figs. 3 and 4. After splenorenal anastomosis, on the other

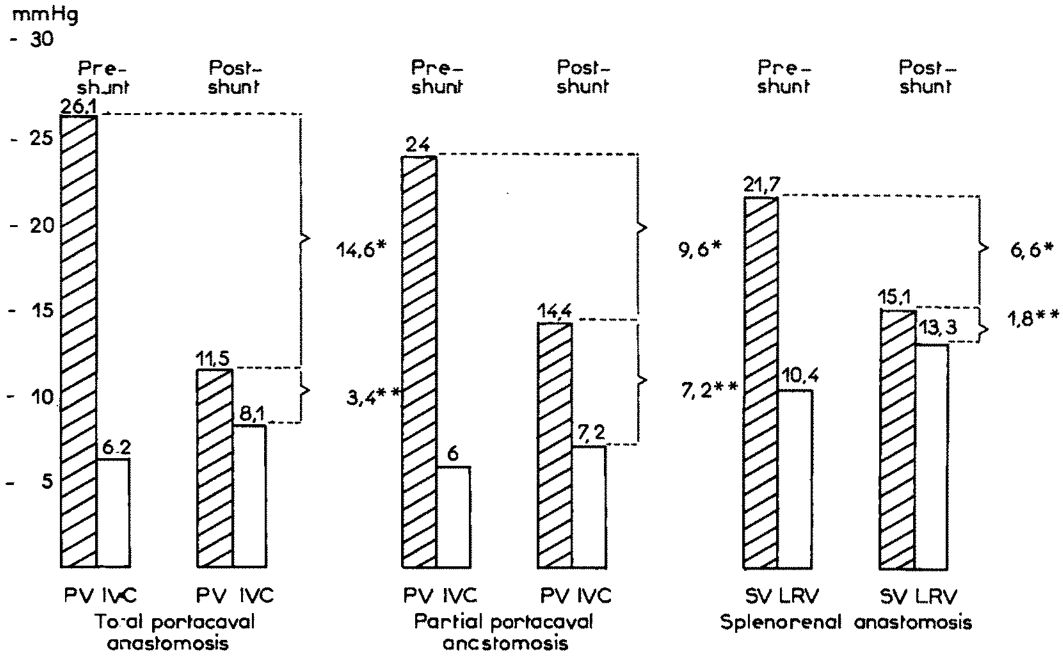

FIG. 1. Pre-shunt and post-shunt pressures (in mm Hg) after total direct portacaval anastomosis in 25 patients, partial direct portacaval anastomosis in 23 patients, and splenorenal anastomosis in 72 patients. P.V. = portal vein pressure. I.V.C. = inferior vena cava pressure. S.V. = splenic vein pressure. L.R.V. = left renal vein pressure. * Fall in portal (or splenic) vein pressure. ** Portacaval (or splenorenal) pressure gradient after shunt.

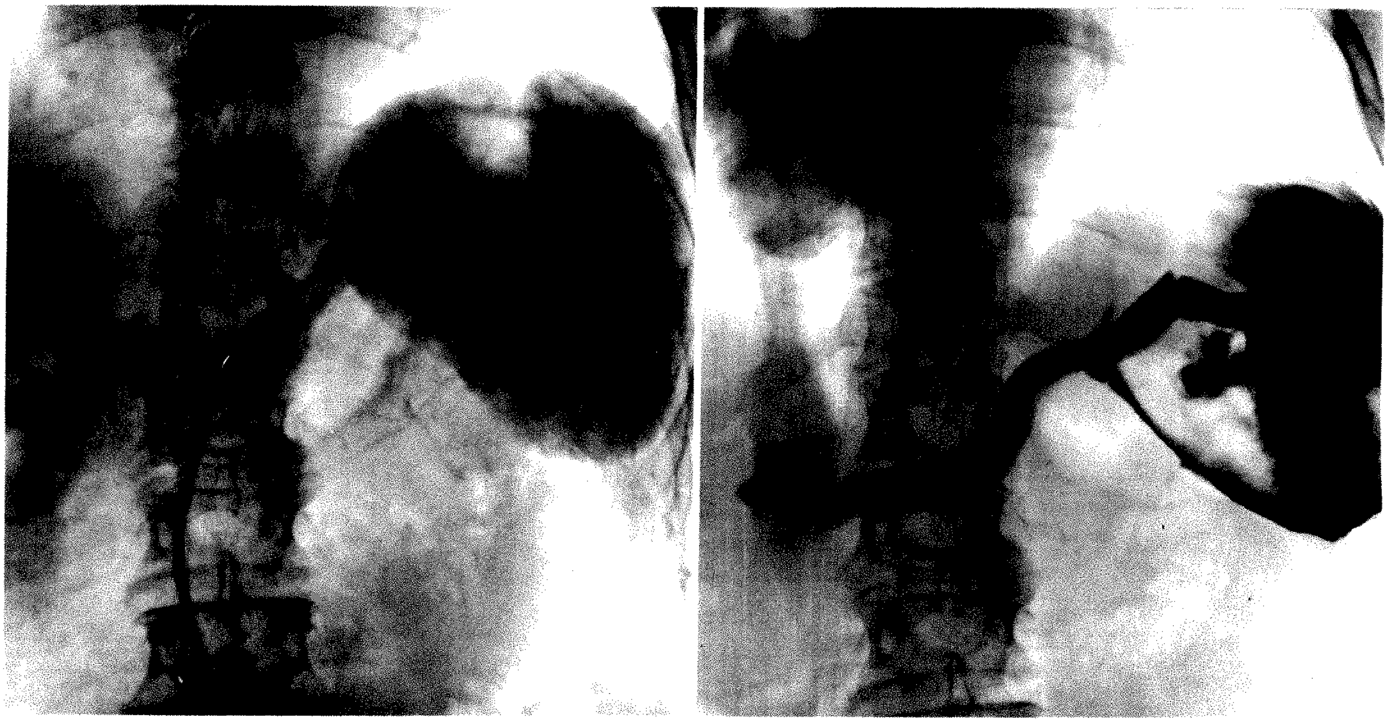

FIG. 3. Partial direct portacaval anastomosis. Postoperative angiographic follow-up study. a. Celiac arteriography, venous phase. The portal vein and its intrahepatic branches are visualized. b. Splenoportography. The portal vein is not visualized. All the contrast medium enters the vena cava.

hand, 2 types of hemodynamic pattern were observed, partial diversion of portal blood (Fig. 5) and total diversion of portal blood (Fig. 6).

Mortality. To the time of writing, 30 patients (25%) have died, 2 (1.6%) during the first 60 postoperative days and 28 (23.4%) at a later date. The operative mortality was nil.

Postoperative Mortality. The 2 patients who died during the immediate postoperative period, arbitrarily defined as the first 2 months after operation, were among

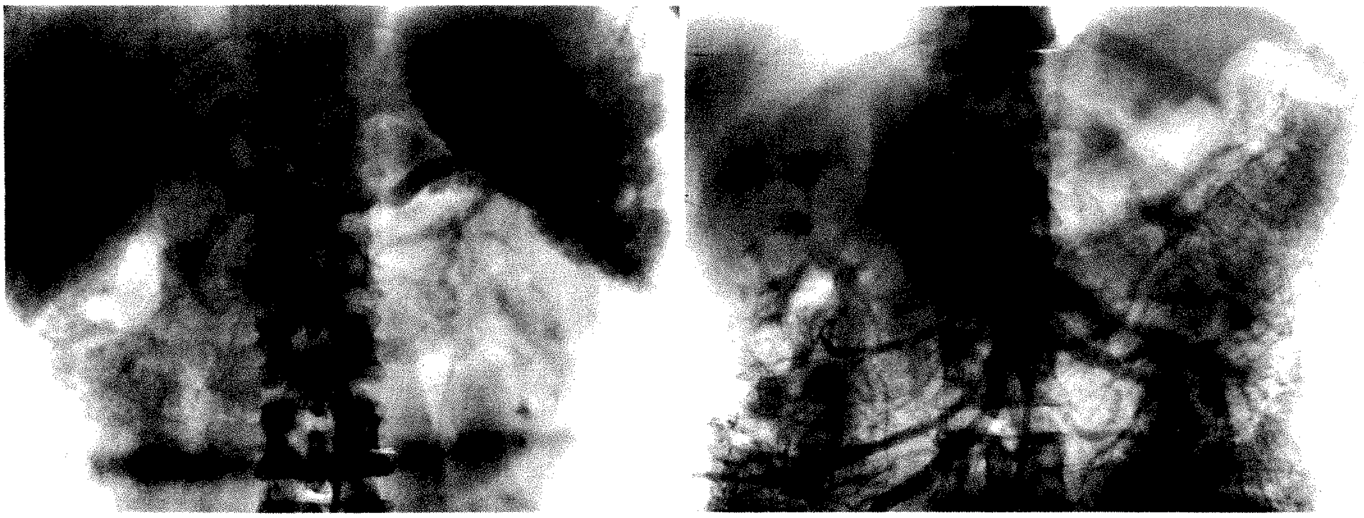

FIG. 4. Partial direct portacaval anastomosis. Postoperative angiographic follow-up study. a. Celiac arteriography, venous phase. The portal vein is opacified. b. Superior mesenteric arteriography, venous phase. Contrast medium is passing from the superior mesenteric vein into the vena cava.

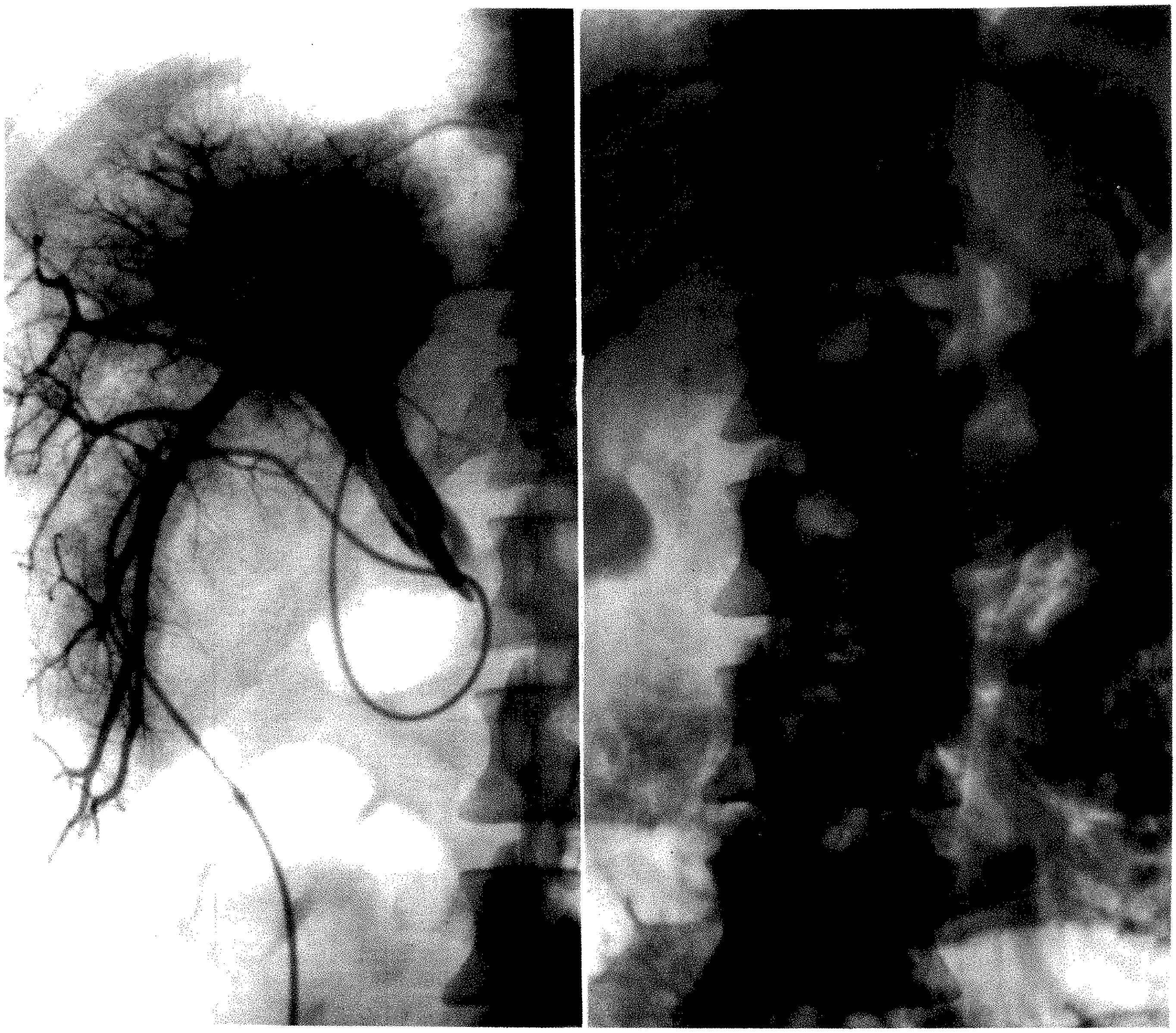

FIG. 5. Splenorenal anastomosis producing partial deviation of portal flow. Postoperative angiographic follow-up study. a. Umbilicography. The intrahepatic branches of the portal vein are opacified. The splenic vein is not opacified. b. Superior mesenteric arteriography, venous phase. All the contrast medium is flowing from the superior mesenteric vein into the splenic vein.

the first 20 patients operated on in our series of 120. They were a man aged 42 with non-alcoholic cirrhosis in whom septicemia developed 12 hours after splenorenal anastomosis and who died on the fourth postoperative day, and a man aged 46 with alcoholic cirrhosis who died from renal failure and ascites 17 days after end-to-side portacaval anastomosis.

Long-term Survival. Survival rates (Figs. 7 and 8) were computed by the actuarial method of analysis described by Cutler and Ederer.[9] Five-year survival was 65.9% for the whole series: 69.7% for total portacaval anastomosis; 65.8% for partial portacaval anastomosis; and 65.4% for splenorenal anastomosis. The differences between the groups are not statistically significant.

The principal non-immediate cause of death (Table 4) was hepatocellular failure, which was responsible for 60.7% of the deaths in the whole series. The group in which hepatocellular failure was most lethal was the splenorenal anastomosis group, in which it accounted for 70.6% of the deaths; this represented 12 patients, in 3 of whom hepatocellular failure was a consequence of viral hepatitis transmitted by blood transfusion. No deaths were due to recurrent bleeding. There was a statistically significant difference between survival in the "good-risk" patients and in the "poor-risk" patients (73.2% and 52.7% respectively ($P < 0.02$)) (Fig. 9). Patients

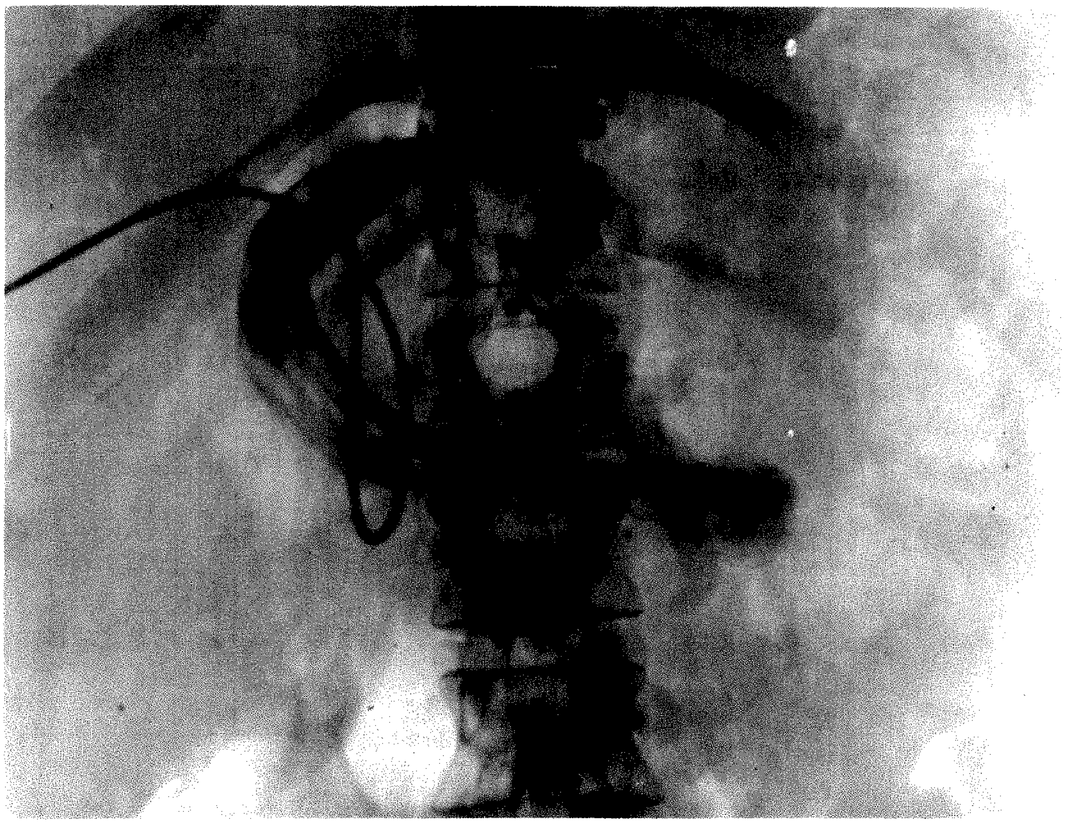

FIG. 6. Splenorenal anastomosis acting as a total shunt. Postoperative angiographic follow-up study. Umbilicography. All the contrast medium is flowing into the portal trunk and the splenic vein. The intrahepatic branches of the portal vein are not opacifed.

over 60 had a slightly better survival rate than patients under 60 (78.1% and 62.8% ($P < 0.05$)) (Fig. 10). Whether the cirrhosis was of alcoholic origin or not appeared to have no effect on survival during the first 2 postoperative years. Thereafter, survival was better in the non-alcoholic group than in the alcoholic group (77.8% and 55.5% ($P < 0.02$)) (Fig. 11). The 5-year survival rate was 88.2% in 31 "good-risk" patients with non-alcoholic cirrhosis, but only 38% in 38 "poor-risk" patients with alcoholic cirrhosis ($P < 0.001$).

Recurrence of Gastrointestinal Hemorrhage. Bleeding recurred in 5 patients (Table 5), all belonging to the splenorenal anastomosis group. In one patient only was recurrent bleeding due to ruptured esophagogastric varices; this patient had thrombosis of his anastomosis, confirmed by angiography.

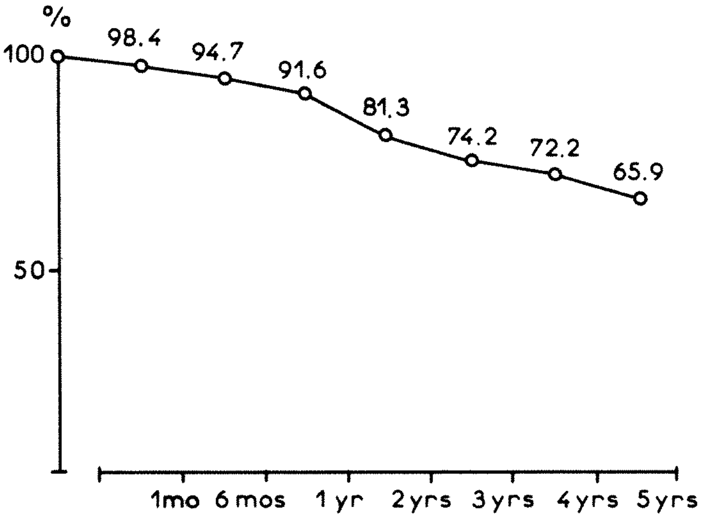

FIG. 7. Five-year survival curve, calculated by the actuarial method of analysis,[9] in 120 patients who underwent portal-systemic shunt operations.

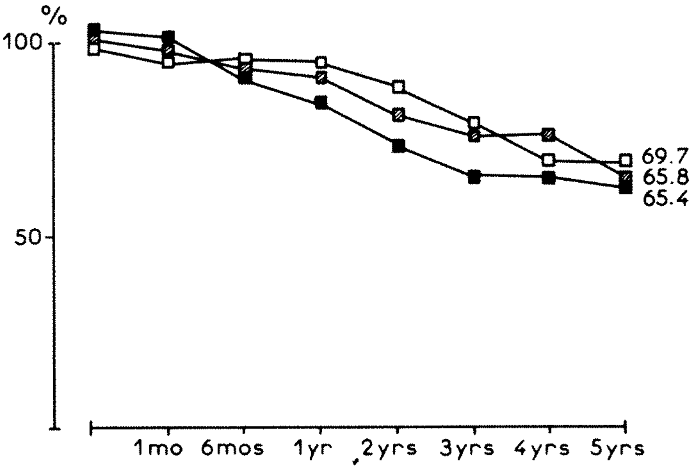

FIG. 8. Five-year survival curves, calculated by the actuarial method of analysis,[9] in 25 patients who had total direct portacaval anastomosis ☐, 23 patients who had partial direct portacaval anastomosis ▨, and 72 patients who had splenorenal anastomosis ■.

TABLE 4. *Causes of Death Later than Second Postoperative Month in 28 of 120 Patients Submitted to Portal-Systemic Shunt*

Type of Shunt	Cause of death				Total Deaths
	Hepatocellular Failure	Hepatoma	Cerebral Hemorrhage	Unknown	
Total portacaval	2 (50)	1 (25)	0	1 (25)	4
Partial portacaval	3 (42.8)	0	1 (14.4)	3 (42.8)	7
Splenorenal	12* (70.6)	1 (5.8)	0	4 (23.6)	17
Total	17 (60.7)	2 (7.2)	1 (3.6)	8 (28.5)	28

It is to be noted that there were no deaths from recurrence of gastrointestinal hemorrhage.
Figures in brackets are percentages.
* In 3 of these patients hepatocellular failure was due to viral hepatitis transmitted by way of blood transfusion.

Esophagogastric Varices. Roentgenographic examination by barium swallow 15 days after operation in 86 patients (Table 6) revealed disappearance of the esophagogastric varices in 65 (75.5%), diminution in 18 (20.9%), and no change in 3 (3.6%). The varices had disappeared in 84% of the patients who had had total direct portacaval anastomosis, in 80% of those with partial direct portacaval anastomosis, but in only 71% of those with splenorenal anastomosis. In 2 of the 3 patients in whom the state of the varices was unchanged angiographic examination disclosed thrombosis of the anastomosis.

Hepatic Encephalopathy. The 14 patients in whom encephalopathy developed constituted 15.5% of the 90 survivors (Table 7). The severity of encephalopathy did not vary appreciably with shunt type. The percentage incidence of the severe form was highest in the patients with small-stoma portacaval anastomosis (6.2%), but this was the smallest group.

Discussion

Many types of portal-systemic shunt have been elaborated, but careful perusal of the literature reveals no outstanding clinical advantages in any of them.

Splenorenal anastomosis has long been regarded as a better procedure than direct portacaval anastomosis. Grace *et al.*,[10] in their analysis of the data in 154 papers, found a lower incidence of encephalopathy after splenorenal shunt (13.4%) than after portacaval shunt (22.2%). Barnes *et al.*[1] found a 5 times lower incidence of fatal liver failure and of shunt encephalopathy in patients selected for splenorenal shunt than in patients selected for portacaval shunt; their 5-year survival was 47% with splenorenal shunt as opposed to 31% with portacaval shunt. However, although these studies showed that the splenorenal shunt had less severe hepatic repercussions than the portacaval shunt, they also showed that it had a higher incidence of recurrent hemorrhage and of thrombosis of the anastomosis. They did not demonstrate a clear-cut relation between the hemodynamic characteristics of shunts and their clinical results.

The better results reported as regards long-term survival and incidence of encephalopathy with splenorenal than with other types of portal-systemic shunt[1,10,11,16] are as yet unexplained. It may be that the low frequency of

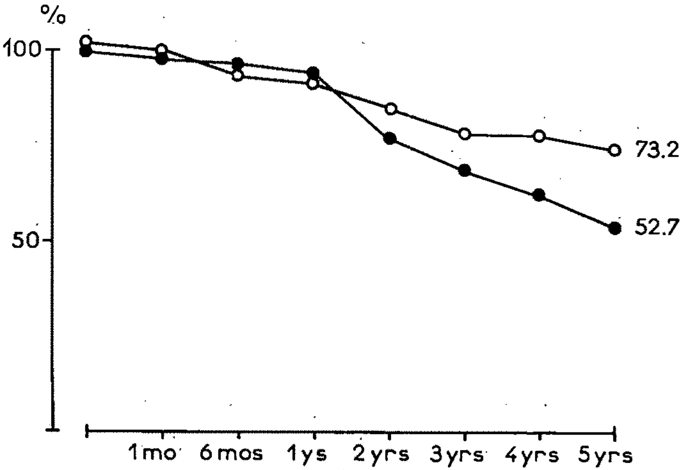

FIG. 9. Five-year survival curves after portal-systemic shunt in 69 "good-risk" patients ○ and 51 "poor-risk" patients ● ($P < 0.02$).

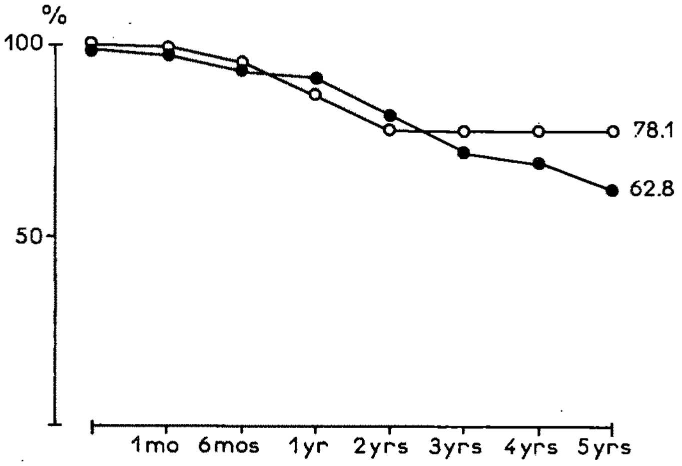

FIG. 10. Five-year survival curves after portal-systemic shunt in 26 patients over age of 60 years at time of operation ○ and 94 patients under age of 60 years at time of operation ● ($P < 0.05$).

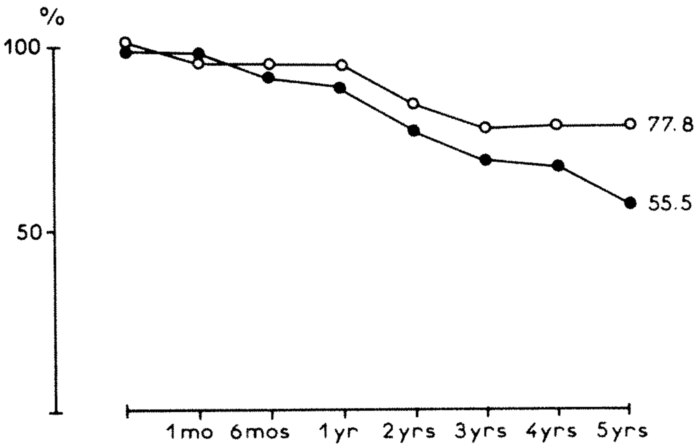

FIG. 11. Five-year survival curves after portal-systemic shunt in 49 patients with non-alcoholic cirrhosis ○ and 71 patients with alcoholic cirrhosis ● ($P < 0.02$).

encephalopathy is due to a high frequency of thrombosis of the anastomosis.

Much work has been done in recent years in devising new shunt techniques, especially in the search for decompressive procedures which would maintain portal perfusion of the liver;[2,6,17,19,22] these techniques include arterialization of the hepatic stump of the portal vein, side-to-side splenorenal shunt, and selective decompression of esophageal varices by a distal splenorenal shunt.

In 1970 Britton and his colleagues[6] reported side-to-side central splenorenal venous anastomosis with preservation of the spleen. It does not emerge clearly from these authors' hemodynamic studies that the deviation was truly selective, or, more specifically, that splenic flow alone was shunted into the systemic system leaving a substantial portal flow to the liver. Their clinical results, moreover, do not plead convincingly in favor of the procedure.

Decompression by a selective distal splenorenal shunt was proposed by Warren *et al.*[22] in 1967, and favorably reported on in a comparative study by Salam *et al.*[19] in 1971. Portal vein perfusion of the liver was well maintained and total hepatic blood flow unchanged or only mildly decreased. There was no long-term mortality, no encephalopathy, and no recurrence of variceal bleeding. However, the number of patients is too small and the follow-up period too short to justify a conclusion that this device for preserving portal flow is superior to large shunts. As the authors say, these studies do not show that hemodynamic differences in shunts exert a significant effect on postoperative morbidity and on longevity.

In our experience, hemodynamics had no discernible effect on the clinical results of portal-systemic shunts. That each of the 3 types of portal-systemic shunt constructed in this study produced its own specific hemodynamic consequences is clear from the pressure readings (Figs. 1 and 2). Equally clear is the fact that early postoperative mortality (2 out of 120), long-term survival, recurrence of gastrointestinal hemorrhage (Table 5), persistence of esophagogastric varices (Table 6), and incidence of encephalopathy (Table 7) were independent of the type of shunt and therefore of the hemodynamic alterations which the shunt had effected.

The hemodynamic consequences of splenorenal anastomosis in our hands were not uniform: in some cases it acted as a partial shunt, in others as a total shunt. The effects depend on several factors, notably the caliber of the splenic and renal veins, and the caliber and technique of the anastomosis. The post-shunt splenorenal pressure gradient in our patients with splenorenal anastomosis was low (1.8 mm Hg (Fig. 1)). Salam *et al.*[19] noted the same phenomenon after splenorenal shunt and attributed it to inability of the left renal vein to accommodate the increased flow without an elevated pressure. Perhaps it is the most important factor in limiting shunt flow in this procedure. On the other hand, if the anastomosis is wide, and centrally placed on the splenic vein, the shunt is liable to have the same effect as a total side-to-side direct portacaval anastomosis, and thus divert all portal blood into the systemic system. The different effects of the shunts illustrated in Figs. 5 and 6 are of interest in this connection. In addition, the hemodynamic effects of a splenorenal shunt may well change after operation. An increase in the caliber of the splenic and renal veins will increase the volume of blood shunted. In one of our patients a 14 mm stoma at operation measured 30 mm at necropsy. These considerations suggest that

TABLE 5. *Recurrence of Gastrointestinal Hemorrhage in 5 of 120 Patients after Portal-Systemic Shunt*

	Cause of Recurrent Hemorrhage				
Type of Shunt	Esophagogastric Varices	Duodenal Ulcer	Aspirin	Unknown	Total Recurrences
Total portacaval	0	0	0	0	0
Partial portacaval	0	0	0	0	0
Splenorenal	1* (1.4)	1 (1.4)	1 (1.4)	2 (2.6)	5 (6.8)
Total	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.7)	5 (4.1)

Figures in brackets are percentages.
* Shunt thrombosed.

TABLE 6. *Status of Esophagogastric Varices as Revealed by Barium Swallow in 86 of 120 Patients on 15th Day after Portal-Systemic Shunt*

Type of Shunt	Status of Varices			Number of Patients
	Disappeared	Reduced	Unchanged	
Total portacaval	16 (84)	3 (16)	0	19
Partial portacaval	12 (80)	3 (20)	0	15
Splenorenal	37 (71)	12 (23)	3* (6)	52
Total	65 (75.5)	18 (20.9)	3 (3.6)	86

Figures in brackets are percentages.
* Shunt thrombosed in 2.

splenorenal anastomosis cannot be utilized for study of the hemodynamic consequences of portal-systemic shunt. Analysis of 2 hemodynamically different shunts, conventional direct portacaval anastomosis and small-stoma side-to-side portacaval anastomosis, discloses no significant difference in the clinical results. It would thus appear that hemodynamic changes are not the chief factor determining the outcome in portal-systemic shunt.

To sum up, it is our view that the volume of portal vein flow in portal deviations is less important than many studies suggest. It is possible, although not yet proven, that in certain cirrhotic subjects, especially those with a high pre-shunt portal flow, the maintenance of a hepatopetal post-shunt portal flow may be beneficial. The practical application of this concept, however, is fraught with difficulty. The ideal would be to select patients for this or that type of shunt according to their preoperative hemodynamics,[15] in particular their portal vein flow, but no method for measuring this before operation has as yet been devised, and current methods for measurement during operation are not altogether reliable. The fashioning of a shunt which would ensure adequate and time-resistant portal venous perfusion of the liver is not easy and is not achieved satisfactorily either by the side-to-side splenorenal anastomosis described by Britton *et al.* or by central splenorenal anastomosis as performed by us. More reliance, one feels, can be placed on the distal splenorenal procedure of Warren and his colleagues, but whether it is practicable in all patients, and whether certain complications inherent in the technique and which are liable to lead to operative and postoperative deaths and to anastomotic thrombosis are within acceptable limits, has yet to be determined.

In parallel with the quest for portal deviation procedures which would be better tolerated by the cirrhotic liver, there has been a steady fall in the postoperative mortality from portal-systemic anastomosis, at least in patients not operated on during episodes of gastrointestinal bleeding. Over the last 2 decades postoperative mortality rates have been reported as follows: in 1955, 23%;[5] in 1966, 17.7%;[10] and in 1970, 10%.[7] The 5-year survival rate has also improved in recent years. In the series reported here early postoperative mortality was 1.6% and 5-year survival was 65.9%.

A further noteworthy feature of this study, and one which is contrary to the experience of many investigators,[12,18] is the better 5-year survival after portal-systemic shunt in patients over 60 years of age (Fig. 10). A possible explanation is that at this time of life cirrhosis is non-progressive. It would thus appear that age is not a contra-indication to a shunting procedure. Like most workers, we found a particularly good life expectancy in patients with non-alcoholic cirrhosis belonging to the "good-risk" group, that is, the group without hepatocellular failure. These facts go to show that complications inherent in hepatic cirrhosis, and the evolution of the disease itself, have an important bearing on the prognosis after portal-systemic shunt.

Encephalopathy was less frequent in our patients than in other series; at 5-year follow-up we had an incidence of 12.5%, which compares favorably with the 57% reported by Voorhees *et al.*[20] Persistent alcoholic indulgence is generally held to be a major factor in the production of encephalopathy in shunted cirrhotic subjects. It may be that the relative facility with which French patients give up alcohol was contributory to the low incidence of encephalopathy in our series. Alcoholism in France is more a misguided social habit than a symptom of deep-rooted psychologic abnormality.

Whatever the reason for these improved figures, they are unlikely to be related to hemodynamic factors, since they emerged independently of the type of portal deviation used. More probably they are attributable to improvement in accessory conditions such as preoperative preparation of the patient, operative technique, in particu-

TABLE 7. *Incidence of Encephalopathy Among 90 Survivors of 120 Patients Submitted to Portal-Systemic Shunt*

Type of Shunt	Grade of encephalopathy*				Total with encephalopathy	Total survivors	Total operated on
	None	Minimal	Moderate	Severe			
Total portacaval	18 (90)	2 (10)	0	0	2 (10)	20	25
Partial portacaval	12 (75)	2 (12.6)	1 (6.2)	1 (6.2)	4 (25)	16	23
Splenorenal	46 (85.1)	4 (7.4)	2 (3.7)	2 (3.7)	8 (14.8)	54	72
Total	76 (84.5)	8 (8.9)	3 (3.3)	3 (3.3)	14 (15.5)	90	120

Figures in brackets are percentages of the 90 survivors.
* As defined by Voorhees *et al.*[26]

lar the use of the abdominal approach, and postoperative care. A variety of non-specific influences, which may at first sight seem to be of minor relevance, may trigger postoperative complications, and some of these may form the starting point of terminal hepatic failure. Preoperative detection of hepatoma, use of Australia-antigen-negative blood for transfusion in order to minimize the risk of hepatitis, frequent follow-up examinations, and surveillance of continued abstention from alcohol, all contribute to better long-term survival statistics, and should not be lost to view in the search for more sophisticated surgical procedures. These latter may produce results which are hemodynamically superior but whose advantages are liable to be annulled by complications inherent in the techniques themselves. Perhaps complex procedures are better tolerated by some patients than by others, but no accurate methods for preselecting such patients are available.

Summary and Conclusions

Portal-systemic shunts have been performed in 120 patients with portal hypertension due to hepatic cirrhosis. Three types of shunt procedure were used: 1) total direct portacaval anastomosis in 25 patients; 2) partial direct portacaval anastomosis in 23 patients; and 3) splenorenal anastomosis in 72 patients. The greatest reduction in portal pressure was obtained with total direct portacaval anastomosis. Although splenorenal anastomosis is, theoretically, a partial portal-systemic shunt, it was found to function in some cases as a total shunt. No significant differences were found between the 3 shunt types as regards postoperative mortality, long-term survival, recurrence of gastrointestinal hemorrhage, persistence of esophagogastric varices, or occurrence of hepatic encephalopathy. Therefore the authors believe that type of shunt and hemodynamic factors are not of primary importance in determining the results of shunting procedures. The results obtained in the study reported here, including an immediate postoperative mortality of 1.6% and a 5-year survival rate of 65.9%, with a very low incidence of recurrent hemorrhage and of encephalopathy, are better than those hitherto reported for portal-systemic shunts in cirrhosis. This is in step with the current general trend towards improved results in the surgery of portal hypertension, a trend which the authors ascribe to better understanding of the disease, better patient management, and more active attempts to eliminate the non-specific factors which augment the mortality and morbidity of the surgical procedure. Efforts to devise shunting techniques which may appear, in theory, to be more effective hemodynamically should not divert attention from these other influences.

References

1. Barnes, B. A., Ackroyd, F. W., Battit, G. E., Kantrowitz, P. A., Schapiro, R. H., Strole, W. E., Jr., Todd, D. P. and McDermott, W. V., Jr.: Elective Portasystemic Shunts: Morbidity and Survival Data. Ann. Surg., **174**:76, 1971.
2. Bismuth, H.: Technique et indications de l'anastomose splénorénale dans les cirrhoses. Ann. Chir., **27**:318, 1973.
3. Bismuth, H., Csillag, M. J., Benhamou, J. P. and Fauvert, R.: L'anastomose porto-cave chez le rat normal. IV. Influence du calibre de l'anastomose. Rev. Fr. Etud. Clin. Biol., **10**:1087, 1965.
4. Bismuth, H., Moreaux, J. and Hepp, J.: L'anastomose splénorénale centrale dans le traitement de l'hypertension portale. Ann. Chir., **20**:1441, 1966.
5. Blakemore, A. H.: The Surgical Treatment of Cirrhosis of the Liver. J. Chronic Dis., **2**:70, 1955.
6. Britton, R. C., Voorhees, A. B., Jr. and Price, J. B., Jr.: Selective Portal Decompression. Surgery, **67**:104, 1970.
7. Callow, A. D., Resnick, R. H., Chalmers, T. C., Ishihara, A. M., Garceau, A. J. and O'Hara, E. T.: Conclusions from a Controlled Trial of the Prophylactic Portacaval Shunt. Surgery, **67**:97, 1970.
8. Clatworthy, H. W., Jr. and Boles, E. T., Jr.: Extrahepatic Portal Bed Block in Children: Pathogenesis and Treatment. Ann. Surg., **150**:371, 1959.
9. Cutler, S. J. and Ederer, F.: Maximum Utilization of the Life Table Method in Analyzing Survival. J. Chronic Dis., **8**:699, 1958.
10. Grace, N. D., Muench, H. and Chalmers, T. C.: The Present Status of Shunts for Portal Hypertension in Cirrhosis. Gastroenterology, **50**:684, 1966.
11. Hallenbeck, G. A., Wollaeger, E. E., Adson, M. A. and Gage, R. P.: Results after Portal-systemic Shunts in 120 Patients with Cirrhosis of the Liver. Surg. Gynecol. Obstet., **116**:435, 1963.
12. Hermann, R. E., Rodriguez, A. E. and McCormack, L. J.: Selection of Patients for Portal-systemic Shunts. JAMA, **196**: 1039, 1966.
13. Jackson, F. C., Perrin, E. B., Felix, W. R. and Smith, A. G.: A Clinical Investigation of the Portacaval Shunt: V. Survival Analysis of the Therapeutic Operation. Ann. Surg., **174**:672, 1971.
14. Jackson, F. C., Perrin, E. B., Smith, A. G., Dagradi, A. E. and Nadal, H. M.: A Clinical Investigation of the Portacaval Shunt. II. Survival Analysis of the Prophylactic Operation. Am. J. Surg., **115**:22, 1968.
15. Kessler, R. E., Tice, D. A. and Zimmon, D. S.: Hemodynamic Factors Reflect Prognosis after Portal Caval Shunt. Surg. Forum, **23**:334, 1972.
16. Linton, R. R., Ellis, D. S. and Geary, J. E.: Critical Comparative Analysis of Early and Late Results of Splenorenal and Direct Portacaval Shunts Performed in 169 Patients with Portal Cirrhosis. Ann. Surg., **154**:446, 1961.
17. Maillard, J. N., Benhamou, J. P. and Rueff, B.: Arterialization of the Liver with Portacaval Shunt in the Treatment of Portal Hypertension due to Intrahepatic Block. Surgery, **67**:883, 1970.
18. Panke, W. F., Rousselot, L. M. and Burchell, A. R.: A Sixteen-year Experience with End-to-Side Portacaval Shunt for Varical Hemorrhage: Analysis of Data and Comparison with Other Types of Portasystemic Anastomoses. Ann. Surg., **168**:957, 1968.
19. Salam, A. A., Warren, W. D., LePage, J. R., Viamonte, M. R., Hutson, D. and Zeppa, R.: Hemodynamic Contrasts Between Selective and Total Portal-systemic Decompression. Ann. Surg., **173**:827, 1971.
20. Voorhees, A. B., Jr., Price, J. B., Jr. and Britton, R. C.: Portasystemic Shunting Procedures for Portal Hypertension. Twenty-six Year Experience in Adults with Cirrhosis of the Liver. Am. J. Surg., **119**:501, 1970.
21. Warren, W. D., Restrepo, J. E., Respess, J. C. and Muller, W. H.: The Importance of Hemodynamic Studies in Management of Portal Hypertension. Ann. Surg., **158**:387, 1963.
22. Warren, W. D., Zeppa, R. and Fomon, J. J.: Selective Transsplenic Decompression of Gastroesophageal Varices by Distal Splenorenal Shunt. Ann. Surg., **166**:437, 1967.

Parenteral Nutrition in the Burned Child:

A Study of Twenty-six Patients

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SEVERE NUTRITIONAL DEFICIENCY and negative nitrogen balance have been well recognized throughout the history of treatment of major thermal burns.[9,10] The expected weight loss in an adult with 40% full thickness burn is 10–20% of the preburn weight, which usually occurs at the rate of 2–5 kg. per week, but may be as high as 1 kg. per day when sepsis occurs.[7,11] Frequently this leads to marked malnutrition which is a major predisposing factor to invasive infection. Attempts to maintain good nutrition via the oral route are limited by the need for frequent anesthesia, ileus associated with septic disorders, risk of aspiration, and poor appetite.

The introduction of effective parenteral feeding by Dudrick, Wilmore, Vars and Rhoads offers a potential solution to this problem.[2] Their techniques of instillation of hyperosmolar solutions of glucose and protein hydrolysate directly into the superior vena cava have proved safe in the general hospital population and to some extent in burns and other patients exceptionally prone to sepsis. The use of this technique in the burned child presents several special problems. These patients have extensive bacterial and fungal colonization of their wounds and adjacent skin, and frequently contaminate the blood stream with these organisms. The subclavian area is often included in the burn wound, making surgical sterility at the puncture site impossible. The child's size, burn wound edema, and contracture of shoulder muscles are impediments to percutaneous venous catheterization. Frequent whirlpool treatments are an obstacle to occlusive dressings.

However, the high mortality and nutritional deficiencies observed in children with large burn wounds have prompted the use of this technique in 26 children.

Method

Patients selected for intravenous nutritional supplementation had acute burns of more than 40% full thickness, or nutritional deficiency as demonstrated by progressive weight loss. All patients were treated by the exposure method with topical Sulfamylon, silver sulfadiazine, or gentamicin. Debridement under anesthesia was begun as soon as eschar began to separate, and porcine heterografts were used from the time of eschar separation until autografting could be accomplished. Systemic antibiotics were given for specific organisms when generalized infection existed.

Intravenous nutritional therapy was begun as soon as the patient's fluid balance stabilized from initial burn shock or when weight loss became a severe problem, and was continued until the patient was able to tolerate a satisfactory oral intake. This was usually the point when most of the open area had been successfully autografted. Rate of administration was pushed to the highest levels tolerated without excessive urinary output or signs of congestive heart failure.

Nutritional fluid was administered by subclavian catheter threaded into the superior vena cava in 15 children who were unburned in this area. Four patients burned over the entire trunk and neck were treated with subclavian catheters through burn eschar with careful placement of Sulfamylon at the site of catheter entrance. Seven patients were treated with cutdown catheters in the jugular, saphenous and basilic veins when the subclavian areas were burned or could not be punctured.

The percutaneous puncture technique was that de-

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TABLE 1. *Nutrient Solutions*

FreAmine	8.5%	500 cc.	Aminosol	5.0%	750 cc.
Dextrose	50%	500 cc.	Dextrose	50%	350 cc.
KCl		30 mEq.	KCl		30 mEq.
NaCl		40 mEq.	NaCl		40 mEq.
Ascorbic Acid		100 mg.	Ascorbic Acid		100 mg.
B Complex		2.0 cc.	B Complex		2.0 cc.
1.18 Cal./cc.			0.91 Cal./cc.		
6.25 gm. N/1000 cc.			4.76 gm. N/1000 cc.		

scribed by Dudrick *et al.*, and was used successfully in children as young as 18 months of age.[2] Catheters were sutured into place and dressed with antibiotic ointment and occlusive dressings. Sites were reprepped and dressed every 3 days or whenever soiled. Medium sized 19 gauge radiopaque catheters were used in children weighing less than 25 kg. with large sized 16 gauge catheters in larger children. Chest X-rays followed all catheter placements to verify position of catheter.

Intravenous catheters remained in place while the patients were without signs of sepsis, and were removed with the onset of signs of sepsis. There were several instances in which catheters were not removed while signs of sepsis persisted because of the difficulty in replacing them or because physicians felt sepsis was originating from burn wounds. This is contraindicated. Intravenous solutions, catheter tips, and blood were cultured routinely when sepsis was suspected.

The nutrient solutions of amino acids, dextrose, vitamins, and electrolytes were mixed carefully on the wards by nursing staff and administered immediately. Standard micro-drop administration sets were used, without micropore filtration apparatus or pumps, in all but 3 patients. A Harvard pump and 22 micron filter system was used for these 3 individuals. FreAmine and Aminosol solutions in the concentrations shown in Table 1 were used in approximately equal amounts. The caloric values of these solutions as 1.18Cal./cc and 0.91Cal./cc, respectively. Electrolyte content of the intravenous fluids was varied as indicated by frequent monitoring of the patient's serum values, with routine addition of sodium and potassium. The serum potassium was maintained above 3.5 mEq/l. This often required more than 100 mEq of KCl daily. One hundred milligrams of ascorbic acid and 2 cc of B Complex preparation was added to each bottle, and patients not eating for long periods were given B_{12} and folic acid. Albumin, plasma or plasmanate was given to keep serum protein levels above 3.0 gm/100 cc and supply trace elements. Whole blood was given to maintain a hematocrit of 40%.

Serum electrolytes, Ca, PO_4, Mg, BUN, FBS, proteins and osmolality were measured every 3 days and more often if clinically indicated. Urine sugars were checked every 6 hours and glucosuria was treated with insulin or a decrease in the rate of administration. Patients were weighed every 3 days except when fresh skin grafts prohibited movement. Preburn weights used in Table 2 were determined from patient histories.

Results

Twenty-six patients with an average burn size of 52% total surface and 37% full thickness were treated with intravenous nutritional therapy for an average of 24.6 days. They ranged in age from 18 months to 14 years.

Fifteen patients gained or maintained weight while being treated, 8 were limited to less than 6.0% weight loss, while 3 had appreciable losses of 15.6%, 24% and 25.7%. The average weight change for the entire series was a decrease of 0.6%. These results and their relation to burn size are summarized in Table 2. The 15 children gaining or maintaining weight averaged 49.6 cc/kg/day of supplementation, which is the equivalent of 3500 Kcal daily in a 70 kg adult. This quantity of supplementation would include 21 gm of nitrogen daily and an ample supply of vitamins in such an adult.

Two patients had radiologic evidence of superior mesenteric artery obstruction of the duodenum and were unable to eat. They lost 22% and 9% of their weight before starting intravenous supplementation. One patient regained 12.4% of his weight while eating only intermittently, and being supplemented, while the other patient received only 27.4 cc/kg/day and lost an additional 5.8% of his weight. Both patients survived. Four other patients had duodenal ulcers demonstrated radiographically by upper G.I. series and ate poorly. After supplementation, 3 of the patients, in spite of impaired oral intake, had a weight loss of less than 6.0% and survived. The fourth patient had severe weight loss of 15.6% during supplementation. She required exploratory laparotomy, vagotomy and pyloroplasty because of hemorrhage, and died with severe burn wound sepsis.

Two other patients, No. 5 with weight loss of 25% of the body weight, and No. 6 with 25.7% weight loss, had

TABLE 2. *Nutritional Results and Relation to Burn Size*

Burn Size—Full Thickness	Number Patients	Average No. Days Therapy	Average cc/Kg/day Therapy	Average % Wt. Change	Mortality
Less than 20%	3	12	41.3	−2 8	0
20–39%	12	21	45.1	+4 3	0
40–59%	8	26	49.3	−5 5	4
Greater than 59%	3	47	45.6	−8.0	3
Average of Total Series	26 (total)	24.6	46.3	−0.6	7 (total)

large deep burns and eventually died after long and extremely septic courses. The course of patient No. 5 is described. Patient No. 6, with a 25.7% weight loss, was a 14-year-old with a 45% burn who was started on supplementation because of a weight loss from 79 kg to 57 kg. He had later sustained an additional loss of 14 kg while unsuccessful attempts were made to control terminal *Pseudomonas aeruginosa* sepsis.

Case Reports

Case 1. A nine-year-old Negro female was admitted 14 days after sustaining a 56% total body surface and 50% full thickness hot gravy burn to her anterior and posterior trunk, legs and arms. The past medical history was unremarkable, and there were no other abnormal physical findings.

She was treated with topical Sulfamylon and supportive fluid therapy. Her wound cultures grew *Enterobacter cloacae* with occasional *Staph. aureus* and *E. coli.* She became toxic from her wounds, ate poorly, and on her 23rd day, a subclavian catheter was inserted through unburned skin and intravenous supplementation begun. Eschar began to separate and multiple debridements were performed. The first autograft using Tanner mesh expanded skin was performed on the 34th postburn day. Further autografting was carried out, and wound coveage was completed on the 90th postburn day. Extensive physical therapy was required and she was discharged on the 150th postburn day.

The initial subclavian catheter was accidentally removed on the 50th postburn day after 26 continuous days of use. During this time she averaged 1700 Cal. daily of intravenous nutrition while her weight fluctuated between 26.8 and 30 kg. Her admission weight was 27 kg and six months postburn she weighed 28 kg. She did not become septic during treatment.

Case 2. This 13-year-old Caucasian female, patient No. 5, was admitted one day after receiving 83% total surface and 78% full thickness burns to her face, neck, anterior and posterior trunk, legs and arms in a house fire. Past medical history and other physical examination were unremarkable.

She was dehydrated on admission and a subclavian catheter was placed through burn eschar, sutured in place and dressed with topical Sulfamylon. Nutritional supplementation was begun on the 4th day. Her wounds were treated with silver sulfadiazine until an allergic rash developed and therapy was changed to topical gentamicin. Multiple debridements under anesthesia were required. Dressings with porcine heterografts were started on the 21st day and continued until death.

An autograft using all available donor sites to the chest, abdomen and neck was performed on the 38th day. The patient's siblings were tissue typed and homograft skin from a brother was applied to legs and arms on the 51st pohtburn day. Immune suppressive therapy consisting of ALG was begun. The grafts took well, and remained viable until death. On the 54th day, autografts recropped from previously used donor sites were applied to the back with fair results.

Parenteral nutrition was continued from the 4th postburn day with supplementation averaging almost 2000 Cal. daily for 59 days. The patient ate intermittenly during this time. Her weight initially increased with burn wound edema, then stabilized at approximately her preburn weight for 36 days of her 59-day course. Carbohydrate intolerance was a persistent problem in spite of 50–100 units of regular insulin daily, and it limited intravenous supplementation to 2500 cc daily.

Sepsis with *Staph. aureus* presented on the 12th day, but responded to sodium oxacillin and a catheter change. Sepsis again became a problem on the 31st day with *Candida albicans, Proteus* and *Klebsiella-Enterobacter* cultured from the blood. This cleared immediately upon removal of the catheter and institution of kanamycin. On the 48th day, blood culture revealed *Candida albicans* and yeast, and the patient's general condition deteriorated. Yeast was cultured from the subclavian catheter and after its removal no further blood cultures revealed fungus or yeast. Blood cultures did, however, continue to reveal *Staph. aureus, Pseudomonas* and *Klebsiella-Enterobacter.* Weight loss over the last 23 days progressed to 24% of preburn weight. She had several episodes of hypernatremia, and jaundice felt to be due to hemolysis developed. She expired on the 65th postburn day.

Postmortem findings included subclavian vein thrombosis which cultured *Staph. aureus, Klebsiella-Enterobacter* and *Pseudomonas aeruginosa.* Pulmonary edema, hemorrhagic pneumonia, septicopyemia of the kidneys, and a diffuse interstitial pancreatitis were also found.

Complications

Seven patients with burns averaging 69% total surface and 58% full thickness died. Postmortem examinations were performed on all patients and organized septic thrombi and were found at the catheter site in 5 patients (Table 3). Two thrombi orginated from jugular cutdowns, and 2 originated from subclavian veins, with propagation into the superior vena cava present in all cases (Fig. 1.) All were adherent to the vein wall and on microscopic section showed organized thrombi colonized

TABLE 3. *Pathology*

Patient	Veins	Culture of Thrombus	Heart	Lungs
1.	Jugular & S.V.C. with organized thrombus	Staph. aureus, Yeast	Tricuspid endocarditis & myocarditis	
2.	Organized thrombus from proximal saphenous to above renal veins	Enterobacter, Staph. aureus, E. coli, Pseudomonas, Candida albicans	Multiple small abscesses	Multiple small emboli
3.	Organized thrombus subclavian and S.V.C.	Pseudomonas	Mitral and tricuspid vegetations, myocardial abscess	
4.	Organized thrombus in jugular vein & S.V.C.	Enterococcus, E. coli, Yeast	Tricuspid endocarditis	Multiple organized pulmonary emboli
5.	Necrotizing phlebitis and organized thrombus in subclavian vein & S.V.C.	Staph. aureus, Yeast	Septic infarct of tricuspid valve	
6.	Normal		Normal	Pulmonary congestion
7.	Normal		Normal	Pulmonary congestion

with yeast and/or bacteria (Fig. 2). One patient, No. 2, developed thrombosis of the inferior vena cava and renal veins while being treated with a proximal saphenous cutdown catheter because of deep burns of his trunk and neck (Fig. 3).

All 5 patients with thrombi also had spetic cardiac lesions. In the 4 patients with superior vena cava catheters, tricuspid valvular lesions were present, and were probably due to the presence of the catheter in the heart. In the fifth patient, No. 2, treated with the inferior vena cava catheter, the catheter tip did not reach the heart and thus the multiple small myocardial abscesses must have been blood-borne. Three patients had multiple small pulmonary emboli, but no evidence of massive pulmonary embolus was observed. All 7 patients died from generalized sepsis which is the usual cause of death in patients with large burns.

Several instances of hypernatremia and glucosuria were noted. Hypernatremia was discovered promptly and was easily treated by slowing nutritional intravenous solution and giving free water. Glucosuria was corrected by slowing intravenous solution and giving insulin.

Two small pneumothoraxes, not requiring chest tubes, were the only complications during the insertion of 50 subclavian catheters. Several catheters turned up into jugular veins and the axillary vein, but simple removal or manipulation of the catheter corrected these situations.

Relations of Pathology to Route of Catheterization

There were no complications in 15 patients treated with percutaneous insertion of subclavian catheters through unburned skin, although one patient died of sepsis and congestive heart failure. Post mortem examination of the subclavian veins and superior vena cava of this patient revealed no sign of thrombosis or phlebitis.

Three of 4 patients treated entirely with subclavian catheters through burn wounds died. Thrombi were found in 2 of these patients who had very large burns and died after 68 and 59 days of continuous therapy. Review of their individual catheter placements shows 4 episodes of sepsis controlled by catheter removal, and that each had a single placement of greater than 22 days immediately preceding death. Post mortem examination of the other patient treated with a subclavian catheter through burn revealed no sign of thrombosis.

In 7 other patients with burns over subclavian areas, long-term insertion of central venous cutdown catheters through unburned skin in other areas was attempted. Three of these patients died after 12, 15 and 30 day courses of therapy, respectively. Thrombus formation occurred, including the one episode of inferior vena cava thrombosis, in all of these patients after 13, 17 and 30-day single catheter placements, respectively.

Sepsis

There were 19 distinct episodes of sepsis during this series, each with at least 3 positive blood cultures, for the same organism. Fourteen of these episodes seemed directly related to the central venous catheters. In 9 of these 14 cases, removal of the catheter caused immediate clearing of the blood cultures and rapid clinical improvement. In the other 5 of these episodes, organized septic thrombus was found at post mortem examination after terminal sepsis.

Five of the 19 total episodes seemed unrelated to the catheters. Removal of the catheter in 3 caused no change

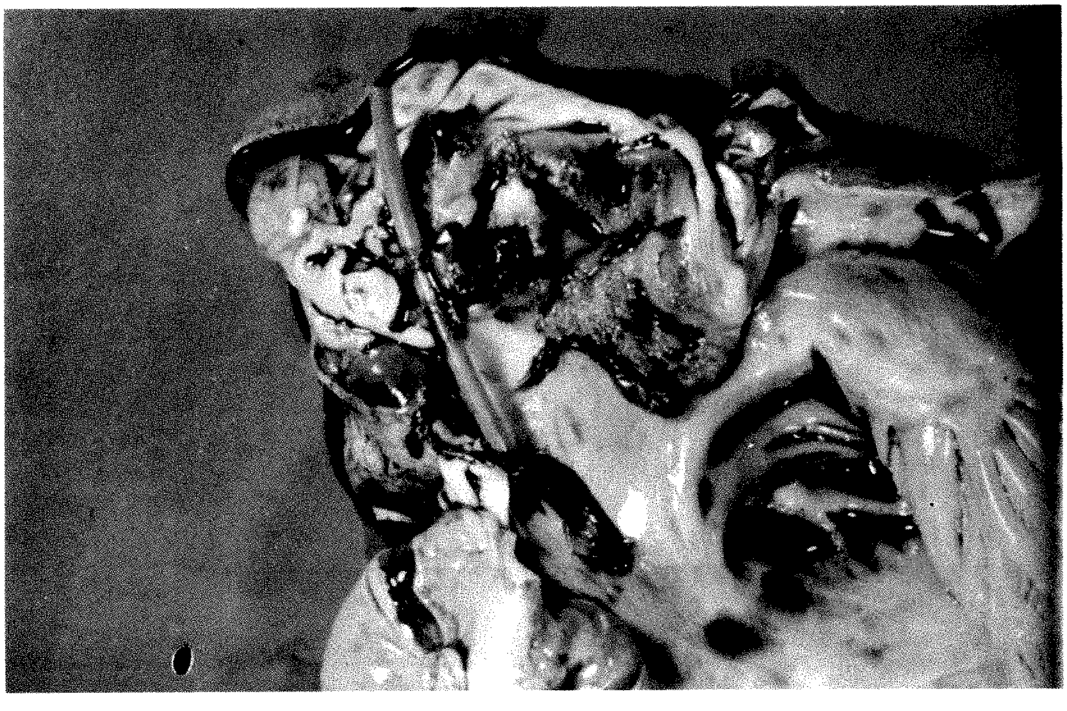

FIG. 1. Organized septic thrombus in superior vena cava originating from jugular cutdown catheter.

and the problem cleared slowly with systemic antibiotics and wound care. The other 2 episodes were terminal, but no thrombus was found at post mortem examination. These results are summarized in Table 4.

The organisms cultured from blood in order of frequency were *Staph. aureus, Pseudomonas aeruginosa, Candida* species, *Enterobacter* species and *Candida albicans.* The flora of the blood consistently corresponded to that of the wound. Cultures of catheter tip grew organisms corresponding to blood cultures in each instance where removal of catheters resulted in control of sepsis.

Of the 19 total episodes of sepsis, 8 involved fungi. Three of these were due to *Candida albicans,* 4 were *Candida* species other than *albicans,* and one involved *Candida albicans* and *Candida* species. Five of these episodes responded to removal of the central venous catheter with complete disappearance of the organism from the blood stream. The other 3 did not respond to removal of the catheter and on post mortem examination, generalized fungal infection was found. One of the other 7 patients who died had generalized candidiasis at autopsy, but never had positive blood cultures. Culture of 4 of the 5 septic thrombi and six catheter tips revealed fungi.

Forty-three cultures of nutritional fluid were collected during episodes of clinical sepsis, and all were sterile. Eight micropore filters were cultured, with 7 being sterile; one grew *Staph. epidermidis,* which was thought to be a contaminant.

Discussion

Evaluation of the nutritional results demonstrated a highly satisfying reduction of the usual weight loss associated with severe thermal burns. Only 3 of 26 patients experienced weight loss approaching the 10–22% level described by Moore and by Wilmore *et al.*[7,11] Unfortunately, the technical problems of measuring the nitrogen content of burn wound exudate made nitrogen balance studies impossible. The quantity of nitrogen (21 gm daily in a 70 kg adult), administered, however, is in the range of the 20.7 to 25.5 gms of nitrogen measured by Soroff, Bearson and Artz to be necessary for equilibrium in somewhat smaller burns (20–35 burn index).[10] It is reasonable to expect that some of these patients with both oral and parenteral intake approached positive nitrogen balance during the catabolic phase. The demonstration of the change in R.Q. from 0.8 to 1.01 by the administration of parenteral nutrition by Wilmore *et al.* in their series of burns is also excellent evidence that the increased nutritional intake is being utilized to spare normal energy stores and tissue in these hypermetabolic patients.[11]

In addition to the objective result, most clinicians thought wound healing and general clinical condition were improved. It is doubtful that patients No. 3 and No. 5 with 62% and 78% full thickness burns, would have survived 75 and 69 days respectively without supplementation even though they both finally died with septic thrombus. Both nutritional solutions in use appeared to

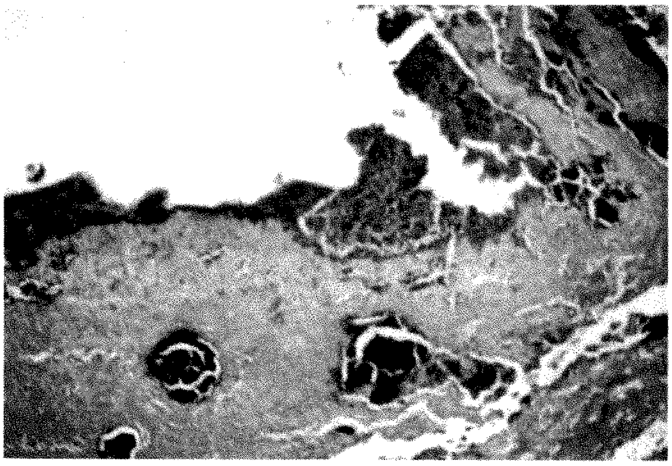

FIG. 2. Photomicrograph of fibrin thrombus colonized with Candida species. Grocott stain 400 ×.

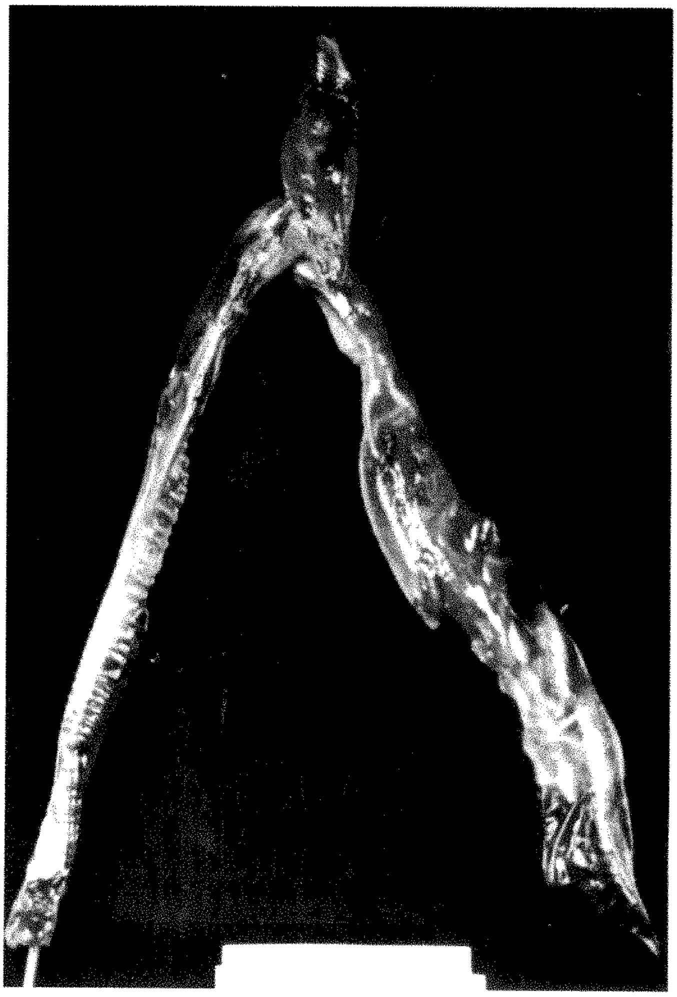

FIG. 3. Iliac and inferior vena cava thrombus originating from proximal saphenous cutdown.

TABLE 4. *Episodes of Sepsis*

Patient	Blood Culture	Catheter Culture	Thrombus Culture	Effect of Removal
1.	Pseudomonas Staph. aureus Klebsiella-Enterobacter Yeast		Staph. aureus Yeast	Postmortem
2.	Staph. aureus Enterobacter		Staph. aureus Enterobacter Pseudomonas C. albicans	Postmortem
3.	Candida albicans	C. albicans E. coli		Sepsis cleared
3.	Pseudomonas	Pseudomonas E. coli	Pseudomonas	Postmortem
4.	Staph. aureus Yeast Enterococcus		E. coli Yeast Enterococcus	Postmortem
5.	Staph. aureus	Staph. aureus Yeast		Sepsis cleared slowly; questionable relation to catheter
5.	C. albicans Proteus Klebsiella-Enterobacter	Proteus Klebsiella-Enterobacter Yeast		Sepsis cleared
5.	C. albicans Yeast	Yeast		Sepsis cleared
5.	Staph. aureus Klebsiella-Enterobacter Pseudomonas		Staph. aureus Yeast	Postmortem
6.	Enterococcus E. coli Enterobacter cloacae	Enterococcus E. coli		Sepsis cleared
6.	Yeast Enterobacter cloacae	Yeast		Sepsis cleared
6.	Enterobacter cloacae Enterococcus	Enterobacter cloacae		Sepsis cleared
6.	Proteus Pseudomonas			None, terminal sepsis
7.	Staph. aureus	Staph. aureus		Sepsis cleared slowly; questionable relation to catheter
7.	C. albicans	Negative		None, terminal sepsis
8.	Yeast	Yeast		Sepsis cleared
9.	Staph. aureus	Staph. aureus		Sepsis cleared; questionable relation to catheter
10.	Klebsiella-Enterobacter	Klebsiella-Enterobacter		Sepsis cleared

be entirely adequate if given in adequate quantity. Results, however, seemed best when supplementation could be given in the absence of severe sepsis, and early use when nutritional problems are anticipated is advantageous.

The frequently described problems with electrolyte balance, hyperosmolar syndromes and glucosuria were encountered, but responded well to therapy. They do not appear to be major problems when recognized and treated promptly.

Preparation of solutions on the wards by nursing personnel immediately before administration proved quite satisfactory. No episodes of sepsis could be related to infected solutions, and no contaminated solutions were found. In-line filtration systems and pumps were not routinely used. Careful training of nursing personnel, observation of patients, and removal of the entire system with the onset of sepsis was adequate management in this series.

Safe administration of nutritional fluid to the patient with large burns including both subclavian areas proved to be the major problem in this group of burned children. The 11 patients with burns of this type accounted for 6 of the 7 deaths, and all of the instances of septic thrombophlebitis. This was in part related to the greater size of the burns (average burn size in patients who died was 69% total body surface and 58% full thickness), but the poor result with techniques of administration other than percutaneously through surgically cleaned skin must be stressed. Both placement of subclavian catheter through burn and attempts at long-term use of cutdown catheters at other portals through clean skin were equally unsatisfactory with each method having approximately the same incidence of septic thrombophlebitis, 50% and 43%, respectively. This is in marked contrast to the experience of 15 patients treated with subclavian catheters through unburned skin without serious complication, which is similar to the experience of most other parenteral nutrition studies.[2,8,11]

The demonstration of the rapid regression of sepsis in most cases when infected catheters are removed suggests this as the primary means of preventing thrombophlebitis. The clinical signs of sepsis are usually dramatic, and catheters remaining in contact with a contaminated blood stream can become infected even if not the underlying cause of sepsis. Rotation of catheters from subclavian to subclavian and possible use of percutaneous internal jugular cannulation or interruption of therapy until sepsis is controlled is probably the best potential management.

The description of these 5 instances of septic thrombophlebitis, the report of 4 other cases by McDonough and Altemeier, and the description of fibrin sleeve formation around catheters by Hoshal *et al.*, should alert the clinician to this possibility of catheter-induced septic thrombophlebitis.[4,6] If sepsis does not resolve following removal of central venous catheters and treatment of other sources of sepsis, the diagnosis can possibly be made pre mortem by venography and treatment by thrombectomy or venous excision attempted.

Development of septic cardiac valvular lesions in the 4 patients with septic thrombi and superior vena cava catheters suggests valvular damage by the technique. In these patients, the catheters were all noted radiographically to have been in the right heart at some time during treatment and the lesions were probably the result of direct catheter trauma or the hyperosmolarity of the solution and the sepsis. This can be prevented by carefully positioning the catheter to extend only into the superior vena cava with post-placement chest X-rays. This will also prevent the perforations of the heart and the hydropericardium described by Fitts *et al.*[3]

The finding that 8 of 19 episodes of sepsis involved fungi and that 4 of 7 deaths had generalized fungal infection demonstrated at autopsy emphasizes the hazard of this type of infection in these patients. An association of *Candida* septicemia in patients undergoing hyperalimentation has been suggested by Ashcraft *et al.*,[1] and the increasing frequency and severity of this hazard in the burned child has recently been described by MacMillan *et al.*[5] Because of the number of variables involved, it is difficult to determine the exact extent to which hyperalimentation influences the incidence of this type of infection. The association of *Candida* infection with hyperalimentation in these patients, however, is readily apparent. This should be recognized by those administering this therapy, and treatment involving removal of intravenous catheters and prompt intravenous therapy with Amphotericin B should be instituted when the problem is suspected.

The possibility of lethal septic thrombophlebitis indicates that nutritional supplementation be used only in those patients in whom severe nutritional depletion might also be fatal. This situation exists in burn patients who undergo weight loss because adequate nutrition via the gastrointestinal system cannot be achieved. With proper care and recognition of the potential problems, intravenous nutritional supplementation is possible and is a valuable adjunct to burn therapy.

Summary

Study of 26 patients with severe thermal burns has demonstrated that intravenous nutritional supplementation can markedly reduce the expected weight loss, and can bring caloric and nitrogen intake up to levels necessary for metabolic equilibrium. No serious problems were encountered in 15 patients when intravenous catheters could be placed through clean unburned skin and standard techniques utilized. A problem with fatal septic thrombophlebitis has been demonstrated in 5 patients with large burns which included both subclavian areas. It is suggested that this might be prevented by rotation of intravenous catheters or temporary removal during periods of sepsis. Septic tricuspid endocarditis resulting from catheter placement in the heart has been demonstrated and can be prevented by careful positioning of catheters in the superior vena cava. Intravenous nutritional supplementation should be considered for all burn patients with severe weight loss due to impaired oral intake.

References

1. Ashcraft, K. and Leape, L.: Candida Sepsis Complicating Parenteral Feeding. J.A.M.A., **212**:454, 1970.
2. Dudrick, S., Wilmore, D., Vars, H. and Rhoads, J. E.: Can Intravenous Feeding as the Sole Means of Nutrition Support Growth in the Child and Restore Weight Loss in an Adult? Ann. Surg., **169**:974, 1969.
3. Fitts, C., Barnett, L., Webb, C., Sexton, J. and Yarbrough, D.: Perforating Wounds of the Heart Caused by Central Venous Catheters. J. Trauma, **10**:764, 1970.
4. Hoshal, V., Ause, R. and Hoskins, P.: Fibrin Sleeve Formation on Indwelling Subclavian Central Venous Catheters. Arch. Surg., **102**:353, 1971.
5. MacMillan, B., Law, E. and Holder, I.: Experience with Candida Infections in the Burn Patient. Arch. Surg., **104**: 509, 1972.
6. McDonough, J. and Altemeier, W.: Subclavian Venous Thrombosis Secondary to Indwelling Catheters. Surg. Gynecol. Obstet., **133**:397, 1971.
7. Moore, F. D.: Metabolic Care of the Surgical Patient. Philadelphia, W. B. Saunders Co., 884, 1959.
8. Rea, W., Wyrick, W., McClelland, R. and Webb, W.: Intravenous Hyperosmolar Alimentation. Arch. Surg., **100**:393, 1970.
9. Reiss, E., Pearson, E., Artz, C. and Balikov, B.: The Metabolic Response to Burns. J. Clin Invest., **35**:62, 1956.
10. Soroff, H., Pearson, E. and Artz, C.: An Estimation of the Nitrogen Requirements for Equilibrium in Burned Patients. Surg. Gynecol. Obstet., **112**:159, 1961.
11. Wilmore, D., Curreri, W., Spitzer, K., Spitzer, M. and Pruitt, B.: Supranormal Dietary Intake in Thermally Injured Hypermetabolic Patients. Surg. Gynecol. Obstet., **132**:881, 1971.

Effect of an Elemental Diet on Gastric Secretion

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ADEQUATE LONG TERM NUTRITION in the seriously ill patient presents the physician with a difficult problem in management. Although total parenteral nutrition can be achieved,[5] the best route for the provision of nutritional requirements is the gastrointestinal tract whenever possible. Gurd and associates[3] showed that the protective role of an elemental diet in reducing the gastrointestinal complications of shock was accompanied by a reduction in pancreatic trypsinogen levels. This has been confirmed by the biochemical and electron microscopic studies reported in the recent paper of Brown *et al.*[4] Since then the use of an elemental diet, has been extended to the treatment of pancreatitis, the short bowel syndrome, ulcerative colitis, biliary and pancreatic fistulae, etc.[12]

This paper considers the effect of an elemental diet on gastric acid secretion in the dog and suggests possible mechanisms for the previously observed reduction in pancreatic enzymes. The diet tested (3200-AS) was generously supplied by Mead-Johnson Laboratories. It contained substantially the same amount of fat, protein and carbohydrate as the dog food use in the control feeds. Its composition (%w/v) was as follows:

Protein (equivalent in amino acids)	9.38
Fat (20% medium chain triglycerides)	14.29
Carbohydrate (by difference)	65.63

Vitamins and minerals were present in adequate quantities in the diet.

Materials and Methods

Pavlov pouches were constructed in anaesthetised mongrel dogs by fashioning a double mucosal septum through a small incision on the greater curvature of the stomach. The pouches were drained by the insertion of a stainless steel cannula in their most dependent part. At least 1 month was allowed for complete recovery from the operative procedure before insulin tests were carried out to confirm good vagal innervation of the pouches. Five dogs were selected for their enthusiasm in consuming the diet.

Twelve control feeds were carried out with 710 g of Romar dog food (Romar Pet Foods Ltd., Willowdale, Ontario), the normal diet for these dogs. Before the control feeds, food was withheld overnight but water was allowed ad libitum.

One day prior to the diet experiments the dogs were fed only with the elemental diet. Test meals of the elemental diet were given on the next 3 consecutive days. The elemental diet was given in liquid form, 1140 ml per test meal, as it is made in a powder and needs to be reconstituted with water. Because of this, water was withheld overnight before testing with the elemental diet. Supplemental feeds of the diet were offered to, and accepted by, the dogs after the collections were finished for the day.

Two 15-minute collections were made before all tests, both control and diet, to ensure the dogs were secreting under basal conditions and then collections were made every 15 minutes for 3 hours after each feed. The volumes of each collection were recorded. The H^+ concentration was measured with a Radiometer TTT2 pH meter and a Radiometer ABU13 Autoburet by titration with 0.1N NaOH to an endpoint of pH 7.0. Sodium and potassium concentrations were estimated with a FLM flame photo-

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meter and the chloride concentration with a Fiske chloridometer.

Statistical analyses were done with the Student t test for unpaired values. Differences are referred to as significant if the probability of their occurrence by chance was less than 5% ($p < 0.05$).

Results

The total 3-hour volume output was reduced from control values of 47.46 ± 3.23 ml to 10.07 ± 1.11 ml, and the total 3-hour hydrogen output was reduced from control values of 6.17 ± 0.50 mEq to 0.71 ± 0.15 mEq.

Not only were the total 3-hour outputs substantially reduced but the individual volume and hydrogen outputs of comparable 15 minute collections were also significantly different (Fig. 1).

It can readily be seen that after the first 15 minutes of feeding there was a marked reduction in both volume and hydrogen ion output and that this was at a high level of significance for each point ($p < .001$). Standard errors of the mean are not shown in the graphs as their values were too small.

The concentrations of hydrogen and sodium ions in the gastric juice are presented in Fig. 2. As the hydrogen ion concentration decreased, the sodium concentration increased. In the control tests a reciprocal arrangements for sodium/hydrogen ion concentration exists and this normal pattern of secretion is not changed by the diet. Although the sodium concentration increased, the volume rate of secretion was reduced to a far greater extent, with the overall effect that the 3-hour sodium output was diminished (control =0.81 ± 0.04 mEq; diet = 0.46 ± 0.05 mEq).

The individual 15-minute post-feed concentrations of potassium and chloride were changed by the diet (Fig. 3). The first 15-minute post-feed chloride concentration was not significantly altered but the second one was just significant at the 5% level ($p < .05$). The differences increased in the second half of the first hour ($p < .005$ and for the remaining 2 hours the post-feed diet concentrations of chloride were markedly reduced ($p < .001$).

On the other hand, the potassium concentrations, except for perhaps a slightly fortuitous difference at 30 minutes ($p < .05$), remained unchanged until the final hour and a quarter of the experiments when some differences were seen (Fig. 3).

In spite of the differing patterns of secretion of potassium and chloride concentration, the total 3-hour potassium and chloride outputs were significantly diminished ($p < .001$), as in the case of sodium, by the overwhelming drop in secretory volume. The total 3-hour potassium output was reduced from 0.39 ± 0.03 mEq to 0.06 ± 0.01 mEq and the chloride output from 7.47 ± 0.54 mEq to 1.24 ± 0.20 mEq.

The table summarizes the results of the changes in the total 3-hour outputs of volume and electrolytes in the gastric juice (Table 1).

Discussion

The success of chemically formulated elemental diets in meeting nutritional requirements has been adequately

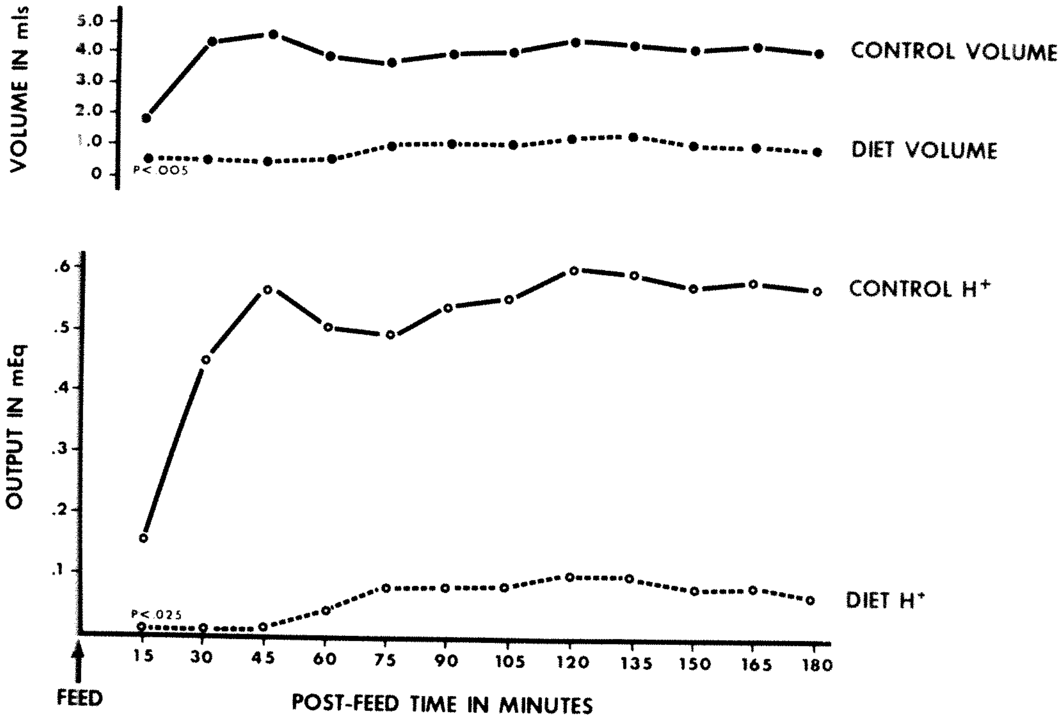

FIG. 1. Volume and hydrogen ion outputs after control and diet feeds. $p < .001$ for all paired values except where indicated.

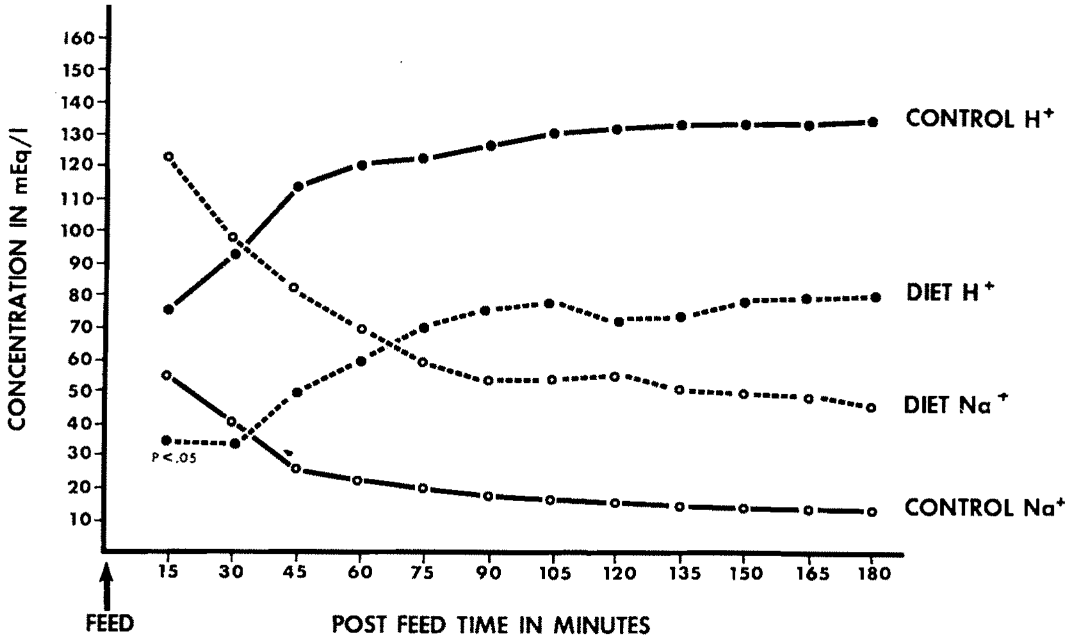

FIG. 2. Concentration of hydrogen and sodium in gastric juice after control and diet feeds. $p < .001$ for all paired values except where indicated.

documented in laboratory animals[1,2,6,7,13,14] and in humans.[4] They possess the advantage of being bulk-free, requiring minimal digestion, and yet providing essential metabolic and caloric requirements. Their protective role seems to stem from their ability to reduce alimentary secretions.

The observed depression in gastric secretion could be the result of a reduction in the cephalic phase of gastric secretion or by the reduced local stimulatory effects of the pre-digested diet or both. It has been known for a long time[8] that the more tempting the diet the greater the gastric secretory response. Although the diet was enthusiastically consumed by the dogs, they would almost certainly have received greater cephalic stimulation from normal canned dog food. It is not unreasonable to suppose that the lowered cephalic stimulation via the vagus

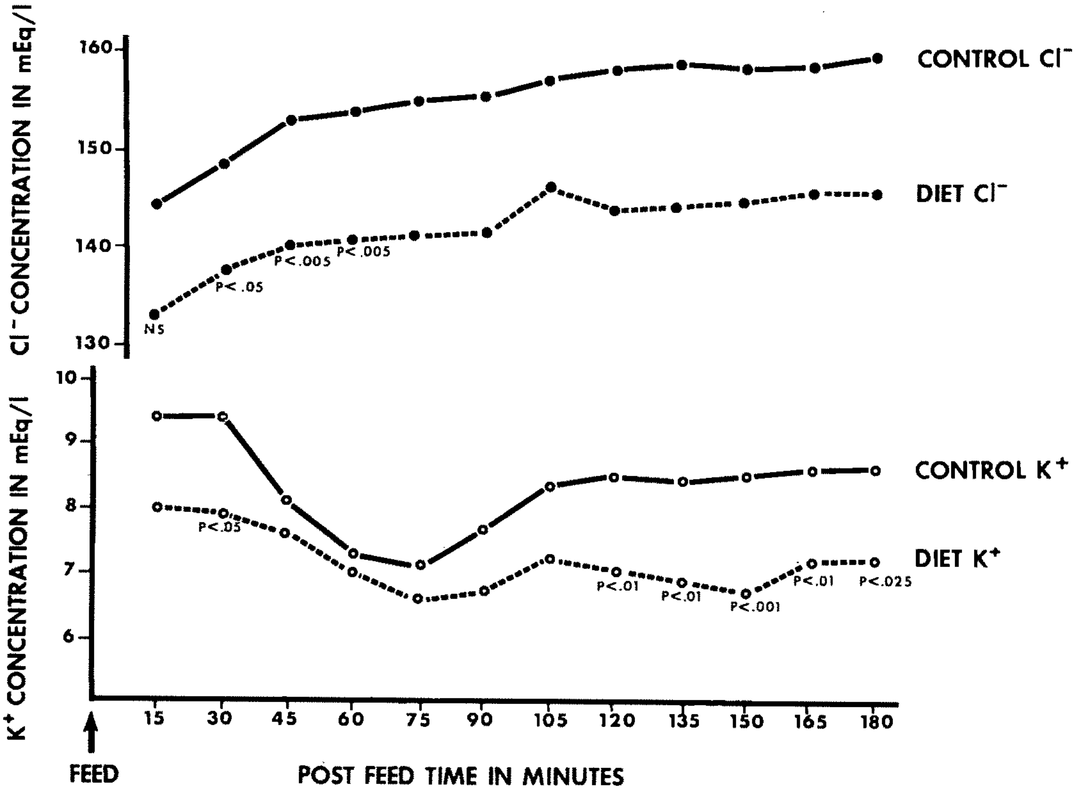

FIG. 3. Concentration of potassium and chloride in gastric juice after control and diet feeds. For chloride curve $p < .001$ for all paired points unless otherwise indicated. For potassium curve $p =$ NS for all paired points unless otherwise indicated.

TABLE 1. *Total 3-hour Volume and Electrolyte Outputs after Control and Diet Feeds*

	Control	Diet
Volume (in mls)	47.46 ± 3.23	10.07 ± 1.11
H^+ (mEq)	6.17 ± 0.50	0.71 ± 0.15
Na^+ (mEq)	0.81 ± 0.04	0.46 ± 0.05
K^+ (mEq)	0.39 ± 0.03	0.06 ± 0.01
Total + ve ions (mEq)	7.37	1.23
Cl^- (mEq)	7.47 ± 0.54	1.24 ± 0.20

$p < .001$ for all paired values

was partly responsible for the observed reduction in gastric acid secretion. The reduced vagal impulses would be expected to affect the pancreas directly, and also indirectly by the reduction in antral gastrin release (see later).

An adequate intake of the elemental diet presents problems in oral feeding, both in ill patients and in healthy volunteers, in spite of its being made in various flavours. It is usually administered by a fine polyethylene infant feeding catheter which is well tolerated by the patient and causes no apparent discomfort. This mode of feeds may be beneficial as it minimizes even further the cephalic phases of gastric and pancreatic secretion. Furthermore, the presence of hydrolyzed proteins could be expected to stimulate little pancreozymin release and to place fewer energy requirements on the alimentary tract for their digestion, compared with the larger protein molecules in a normal diet.

Pancreatic secretion is mainly evoked by the release of secretin and pancreozymin from the upper small intestine as well as by vagal stimulation and antral gastrin release.[10,11] The release of these hormones is brought about by the presence of acid chyme in the duodenum and upper small intestine. This study showed that the elemental diet produced a five-fold reduction in the volume of gastric juice, and an eight-fold reduction in hydrogen ion output due to a concomitant decrease in hydrogen ion concentration. These observed reductions in volume and acid output should reduce exocrine pancreatic secretion and may provide an explanation for the reduction in protease storage in the pancreas.[4] All the above mechanisms probably also involve the complete range of alimentary secretions including biliary secretion.

An interesting finding in the trial experiments with the dogs who were rejected from this study because they ate the diet erratically or unenthusiastically, was that the volume ingested was not related to the gastric juice produced, i.e., the same dog could produce a larger quantity of gastric juice on a smaller intake of the diet and on another day produce a minimal response after complete ingestion of the offered diet. This suggests that the volume of ingested nutrients plays little or no part in the normal physiological response to a meal and is in agreement with recent similar observations by Kaye.[9]

Summary

An elemental diet (Mead-Johnson 3200AS) has been shown to markedly decrease gastric acid secretion. A hypothesis has been put forward to explain the probable mechanisms whereby this leads to a reduction of all the other alimentary exocrine secretions, especially pancreatic secretion. Because of these widespread effects, yet with the retention of an adequate nutritional capability, the diet should prove to be of value in a variety of surgical conditions.

References

1. Birnbaum, S. M., Greenstein, J. P. and Winitz, M.: Quantitative Nutritional Studies with Water Soluble Chemically Defined Diets: II. Nitrogen Balance and Metabolism. Arch. Biochem. Biophys., **72**:417, 1957.
2. Birnbaum, S. M., Winitz, M. and Greenstein, J. P.: Quantitative Nutritional Studies with Water Soluble Chemically Defined Diets: III. Individual Amino Acids as Sources of "Non-Essential" Nitrogen. Arch. Biochem. Biophys., **72**: 428, 1957.
3. Bounous, G., Sutherland, N. G., McArdle, A. H. and Gurd, F. N.: The Prophylactic Use of an "Elemental Diet" in Experimental Hemorrhagic Shock and Intestinal Ischaemia. Ann. Surg., **166**:312, 1967.
4. Brown, R. A., Thompson, A. G., McArdle, A. H. and Gurd, F. N.: Alteration of Exocrine Pancreatic Storage Enzymes by Feeding on an Elemental Diet: A Biochemical and Ultrastructural Study. Surg. Forum, **21**:391, 1970.
5. Dudrick, S. J., Wilmore, D. W., Vars, H. M. and Rhoads, J. E.: Long Term Total Parenteral Nutrition with Growth, Development and Positive Nitrogen Balance. Surg., **64**: 134, 1968.
6. Greenstein, J. P., Birnbaum, S. M., Winitz, M. and Otey, M. C.: Quantitative Nutritional Studies with Water Soluble, Chemically Defined Diets: I. Growth, Reproduction and Lactation in Rats. Arch. Biochem. Biophys., **72**:396, 1957.
7. Greenstein, J. P., Otey, M. C., Birnbaum, S. M. and Winitz, M.: Quantitative Nutritional Studies with Water Soluble Chemically Defined Diets: X. Formulation of a Nutritionally Complete Liquid Diet. J. Nat. Cancer Inst., **24**:211, 1960.
8. Janowitz, H. D., Hollander, F., Orringer, D., Levy, M. H., Winkelstein, A., Kaufman, R. and Margolin, S. G.: A Quantitative Study of the Gastric Secretory Response to Sham Feeding in a Human Subject. Gastroenterology, **16**: 104, 1950.
9. Kaye, M. D.: Measurement of Gastric Acid Secretion in the Rat by Test Meal: Effect of Distention, Pentagastrin and Propantheline. Am. J. Dig. Dis., **16**:9, 1971.
10. Preshaw, R. M. and Grossman, M. I.: Stimulation of Pancreatic Secretion by Extracts of the Pyloric Area of the Stomach. Gastroenterology, **48**:36, 1965.
11. Preshaw, R. M., Cooke, A. R. and Grossman, M. I: Stimulation of Pancreatic Secretion by a Humoral Agent from the Pyloric Gland Area of the Stomach. Gastroenterology, **49**: 617, 1965.
12. Stephens, R. V. and Randall, H. T.: Use of a Concentrated Balanced Liquid Elemental Diet for Nutritional Management of Catabolic States. Ann. Surg., **170**:642, 1969.
13. Winitz, M., Birnbaum, S. H. and Greenstein, J. P.: Quantitative Nutritional Studies with Water Soluble Chemically Defined Diets: IV. Influence of Various Carbohydrates on Growth with Special Reference to D-Glucosamine. Arch. Biochem. Biophys., **72**:437, 1957.
14. Winitz, M., Greenstein, J. P. and Birnbaum, S. M.: Quantitative Nutritional Studies with Water Soluble Chemically Defined Diets: V. Role of the Isomeric Arginines in Growth. Arch. Biochem. Biophys., **72**:448, 1957.

Carbon Dioxide Laser Débridement of Decubitus Ulcers:

Followed by Immediate Rotation Flap or Skin Graft Closure

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THE TREATMENT OF DECUBITUS ULCERS continues to be a distressing and discouraging task. The standard method used throughout the world today is divided into two stages. In phase one, a variety of preparations is employed to clean the area of infected material, liquid pus, and as much of the necrotic tissue as possible. Antibiotic, bactericidal and bacteriostatic agents, enzymes, dehydrating crystals (such as urea and sucrose), powders, chlorophyll ointments and everyday washes, such as saline or chlorine solutions, are used on more or less empirical grounds daily for weeks and even months, all in preparation for definitive surgical closure.

In phase two, debridement with scalpel and, at times, cautery knife prepares the always contaminated and, most often still infected bed, for rotation flap closure. Skin grafting is sometimes used when flaps are unavailable, for example with decubiti on the heel, but has the disadvantage of too thin a covering for an area where pressure is likely to recur. If bony prominences protrude into the ulcerated region, these must be shaved down or removed. Where the ulcer is deep, muscle rotation flaps are useful[1,2,6] and these will then accept skin flaps or grafts. With conventional surgery, as described above, blood loss is a serious problem, especially in the chronically ill, usually neurologically impaired, young paraplegic or quadriplegic patients. Blood loss is equally serious for the elderly, often demented and debilitated patients in whom decubiti frequently develop.

As a result, during phase one, infection depletes the patient's anatomical and physiological resources, for example, by producing secondary anemia; the patient is exposed to the possible spread of infection; fluids, proteins and electrolytes are lost; catheterization of the urinary bladder becomes mandatory; skilled nursing personnel are required for frequent attention; hospitalization is prolonged; rehabilitation measures are delayed unduly; and high costs skyrocket further. As if this were not enough, disabling and, at times, painful muscular spasms, contractures of joints, osteoporosis with kidney stone formation and loss of vasomotor control will supervene when, as usual, the decubiti prevent ambulation or mobilization.

Treatment of decubitus ulcers by immediate surgical debridement of conventional type has never found favor when necrotic material is extensive and adherent and because of the presence of infection, the inability to prepare the bed of the ulcer to accept a rotation flap or skin graft, and the knowledge that under such circumstances the closure will fail, leaving the patient in the same position after surgery as before. In any case, the anticipated blood loss deters the hand of most surgeons. What is needed, is a method which 1) efficiently removes dead tissue, even including bone, 2) is hemostatic, and 3) leaves a healthy bed capable of accepting flaps or grafts or which granulates nicely to permit closure by epitheliali-

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zation, when the ulcer is small. We believe that the carbon dioxide laser provides these 3 essential factors.

Background

Studies with the laser by the senior author over the past 10 years led to the present concepts underlying laser debridement of decubitus ulcers. It was first noted during the CO_2 laser vaporization of transplantable brain tumors in mice that ulcerated areas were as well treated as nonulcerated areas. It did not matter that crusts, dried blood, pus or remaining skin with fur were present. These could all be vaporized away without difficulty and closure of the skin over these previously infected areas occurred in 100% of the animals. We then attempted to create bed sores in animals but, as expected, could not produce ulcers comparable to those found in patients. As a substitute for such a model we carried out with colleagues,[4,9,10] a series of tests of laser debridement of acute third degree experimental burns in pigs and found that these could be removed cleanly and hemostatically. More important still was the highly successful series of "takes" of immediate autografts on the laser debrided areas. Thus far a single successful human case has also been treated. The senior author has also shown the feasibility of the method in 2 human cases of neoplasm; one a brain tumor and one a metastatic laryngeal tumor.[7] He has, with colleagues[8] treated with surprising success, a chronic thermal ulcer in a dog in which, over an 11-month period of hospitalization, all previous medical treatment and six surgical procedures had uniformly failed to result in permanent closure. With all of this experience behind us we embarked upon the present study in human cases, knowing that the method was safe and almost certain of success.

The carbon dioxide laser[12] is one of a class of new devices that produces coherent electromagnetic radiation of high intensity, in this case at 10.6 microns in the far infrared region of the spectrum. At this wave length, absorption is nearly complete in water and, therefore, in all biological tissues. The laser beam is built up extremely rapidly by electrical excitation within a partially evacuated gas tube containing carbon dioxide, nitrogen and helium. The electrical "pumping" rapidly raises the excitable molecules of CO_2 from ground state to higher energy levels from which they drop in large numbers all at once to a lower level, at an energy difference productive of billions of photons at 10.6 microns wave-length. This occurs when by amplification more than 50% of the molecules have been excited, the so-called "population inversion", and this condition is more rapidly reached in the presence of excited nitrogen molecules, whose levels are close enough to those of carbon dioxide to exchange energy with the latter. The helium aids largely by removing heat. The coherent beam so produced has all its waves in phase both spatially and temporally and is not only intense but nearly monochromatic. The beam diverges very little, can travel for long distances unless absorbed and can be reflected, refracted or focused by appropriate lenses and mirrors.

The CO_2 laser beam has been shown by the senior author to possess in its action on biological tissue, 2 properties of surgical value. The first, its ability to vaporize tissue, is not available to surgeons by any other means except on a very limited scale. The high frequency radio-cautery cuts by vaporizing only in a thin line, and the plasma knife is reported to vaporize but has produced gas embolization. Only the CO_2 and argon lasers vaporize tissue and in our own earlier studies the former has clearly demonstrated its ability to remove large masses of tissue rapidly and efficiently. By vaporization is meant conversion of solid tissue such as necrotic material, or for that matter, semisolid liquids such as pus, to smoke and gas. The vapor is then removed from the operative field by strong suction.

The second surgically important property of the CO_2 laser is its hemostatic action, an action based on the intense heat of the beam and resulting in coagulation of vessels. In removal of dead tissues from decubitus ulcers, the CO_2 laser beam is virtually 100% hemostatic, provided proper intensity, correct degree of focusing for the power output employed and the tissue being vaporized, and proper surgical technique of beam application are utilized. Thus employed, the CO_2 laser produces no damage whatsoever at a distance and, in fact, as shown by light and electron microscopy[11] as well as temperature measurements adjacent to CO_2 laser incisions,[3] leaves tissue one half-millimeter away, or less, undamaged. Sweeping the beam rapidly over the material to be removed prevents penetration beyond the desired depth. By raising the power and widening the focus, large areas can be treated in broad sweeps, while maintaining excellent control. Debridement proceeds rapidly. Should bleeding occur, as will happen when a focused beam meets a large vessel and penetrates it, the laser can quickly coagulate by being moved toward or away from the target to broaden the focus and envelop the bleeding point. When necessary, of course, a clamp and tie can be applied as usual for conventional surgery. The material is then removed slowly or rapidly and layer by layer until normal tissue is reached.

In proper hands, the CO_2 laser is safe. Laser radiation at 10.6 microns is stopped by glass and, therefore, ordinary eyeglasses with their corrective lenses or plain glass will protect the eyes from direct entry of the beam. Such entry would otherwise severely damage the cornea and other media not transparent to this wave length. Plastic goggles are also available. The beam should not be allowed to impinge upon metal instruments to avoid unsuspected reflections and, for that matter, to prevent damage to delicate instruments. Flammable materials, such as plastic drapes, should not be used and ordinary cloth materials must not come into contact with the beam unless they are wet. In that case, all water at the site of application must evaporate before ignition can take place. Gauze sponges soaked in water or saline placed around the ulcer will give adequate protection. Most important, of course, is the handling of the instrument by skilled surgeons.

Methods

The Instrument

The CO_2 laser we employed is a compact unit largely contained in a single, standard, electronic cabinet with a specially built jointed surgical arm through which the beam is reflected and focused on to the target. It was designed and built by Dr. Thomas Polanyi and Mr. Herbert Bredemeier, Physicists at the American Optical Corporation Research Laboratories in Framingham, Massachusetts. They have collaborated closely with us in all of the studies cited above as well as in the present effort. This laser has been fully described in previous publications.[5] It delivers virtually continuous-wave, infrared radiation at nearly pure 10.6 micron wave length, with continuously variable power yielding from zero to 100 watts at the exit end of the handpieces. The latter are interchangeable for near and far focus and are easily prepared in the gas sterilizer. Aiming lights and a clock timer are included. Two tanks of the properly proportioned CO_2, N_2 and He gases are ready for use in the rear of the cabinet and power supply is via a single cable employing 110 volt A.C. current from a 30 ampere receptacle. Tap water cooling is needed to dissipate the heat of the gas discharge tube. The rotary joints at the end of the surgical arm to which the handpiece and its focusing lens is attached, provide easily controlled motion in all 3 dimensions. A footpedal switch allows the surgeon to have complete control of the output application.

Surgical Technique

General principles have been given above. In the present cases reported, the surgical technique itself was the same in all patients. General anesthesia was used since the very high temperature of the laser beam would be painful. The ulcer to be debrided and the rotation flap were surgically cleaned with betadine and draped with cloth drapes. The ulcer bed with its necrotic, pustular material and the devitalized, scarred skin edges were all lased away by excision or vaporization using the laser off-focus with a spot 2–4mm. diameter. Medium and high powers were used, generally from 10–80 watts, sweeping the beam continuously back and forth over the entire area. Lasing was interrupted as desired to change power, at times to shift the degree of focusing and whenever necessary to move to another area. Power was reduced as the region of normal skin to be left behind was approached and as the base of the ulcer at normal underlying tissue was reached. In these cases, it was ordinarily not necessary to coagulate additionally with the laser for bleeding since virtually none occurred except where scalpel biopsies were taken. Bony prominences, when present, were removed by direct laser application at high powers.

Rotation flaps were used in the standard manner in 4 of the 5 cases, *i.e.* in all but the ulcer of the heel where a flap was not possible. In that case a mesh skin graft was employed. The rotation flaps were first outlined with methylene blue, then cut with the cold scalpel, next rotated and finally sutured in place. The remaining gap was overcome by undercutting and suturing. In 2 of the 4 patients the lased edges were first excised with the scalpel and scissors before suturing, but in the other 2 they were not and lased edges were sutured to lased or scalpel-cut edges as required by position. Hemovac drains were used for 1–2 days in each of the 4 flap rotations. Following operation, the usual protective nursing care was given to avoid pressure on the operative site.

Ancillary studies for bacterial testing and microscopic analysis were done by taking specimens before, during and after lasing.

Color photography was used to document the laser action and the results during and after lasing, as well as for postoperative follow-up to show healing.

Case Material

The first patient underwent laser surgery on January 27, 1972. There were, in all, 5 decubitus ulcers in 4 patients. Two of the ulcers were in a 19-year-old, male patient rendered quadriplegic in an automobile accident, one of these being trochanteric and the other sacral in location. This patient also had diabetes mellitus, difficult to control. Two other patients were women, aged 42 and 48, with multiple sclerosis and the last case concerned a 78-year-old, demented woman with an ulcer of the left heel. All had had their decubiti for many months and previous medical and surgical treatment had failed to bring about healing. Hyperbaric oxygenation was given in 2 of the patients following operation as part of an additional study of its possible value in the treatment of decubitus ulcers. One of these patients (D.B.) received 11 hyperbaric treatments after laser debridement of his sacral ulcer (2nd operation) but not following laser debridement of his trochanteric ulcer (1st operation). These were given twice daily at 2.8 atmospheres absolute for 60 minutes each. The other patient (B.B.), a 42-year-old woman with multiple sclerosis, had only four days of treatment with hyperbaric oxygen given twice a day for a total of eight treatments. These were also given at 2.8 atmospheres absolute for 60 minutes each, beginning two days following surgery.

Case Reports

Case 1. (D.B.) This 19-year-old man, referred by Dr. Richard Sullivan, Kessler Institute for Rehabilitation, West Orange, N.J., had been rendered quadriplegic in an automobile accident 1 year and 3 months prior to his laser debridement for trochanteric decubitus ulcer. This was the first operation in our series and took place on January 27, 1972. The injury also produced prolonged unconsciousness lasting 6–7 days and thereafter he continued to suffer from headaches and occasional convulsions. He used 65 units of Lente Insulin every day and diabetes was quite difficult to control. Neurologically, he had no motion in the legs or hands and showed marked weakness throughout both upper extremities with a sensory level bilaterally at C7–8. There was marked but partial loss to T–10 on both sides and total loss below that. A Foley catheter was necessary. On admission he suffered from severe flexor spasms of the legs which were relieved only temporarily by 2 laminectomies for Bischoff's longitudinal myelotomy, but which subsided permanently and completely following subarachnoid alcohol block.

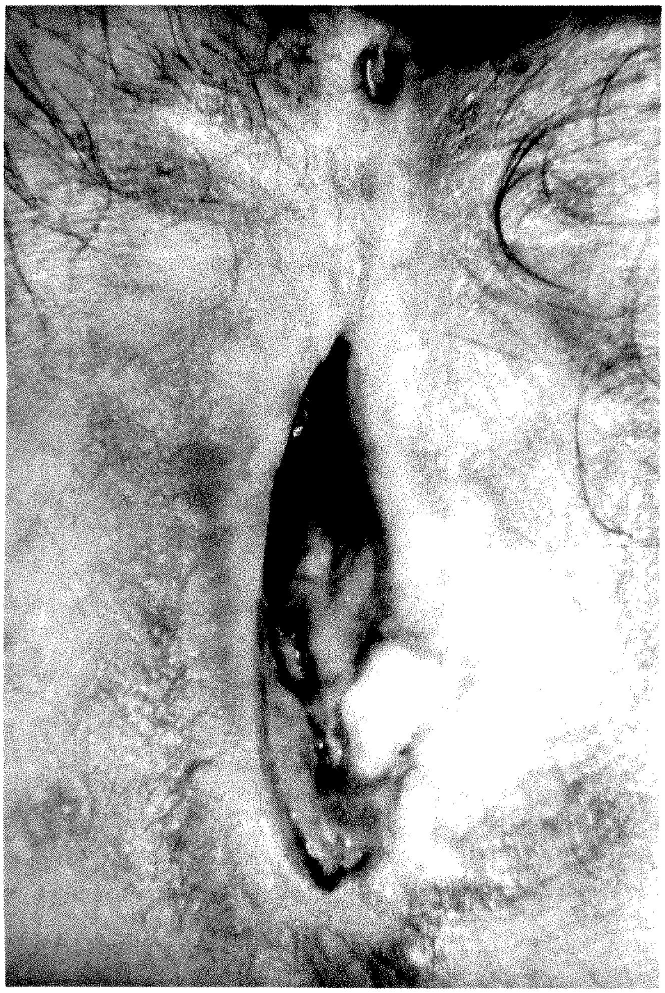

Fig. 1. Sacral decubitus ulcer, before lasing (Case 2, B.B.) showing undermined edges and infected, necrotic material on the ulcer bed.

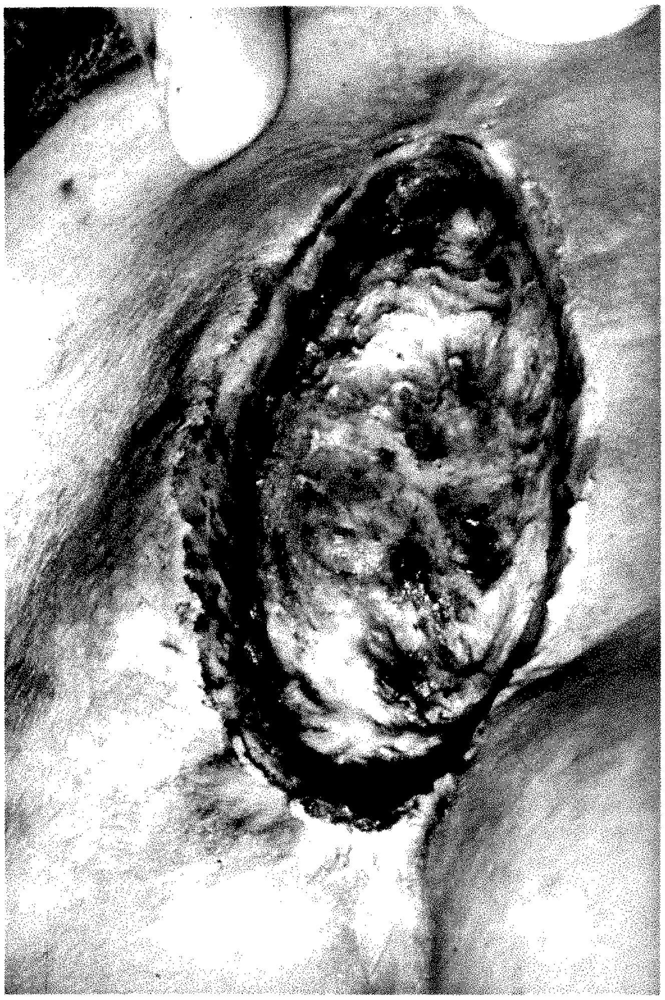

Fig. 2. Same case as Fig. 1, showing ulcer after CO_2 laser debridement. The 3 dark areas represent bleeding spots from which biopsies were taken by the cold scalpel after lasing was completed. There is no bleeding over the rest of the lased bed and edges.

The decubitus ulcer on the left hip measured approximately 4 × 6 cm., with a 2 cm. wide zone of undermined edges. The ulcer extended down to the depth of the trochanter without actually exposing the bone proper. Purulent and necrotic material persisted over much of the ulcer surface even after daily local care. This included daily washing with Phisohex and saline, morning and evening, with measures taken to avoid pressure on the bedsores.

At operation the decubitus ulcer was fully debrided employing the vaporizing properties of the beam starting at 10 watts and gradually increasing to 80 watts. All of the dead tissue and infected material was removed as were the scarred, undermined skin edges. The rounded but protruding greater trochanter was reduced in size using the highest powers of the laser. There was no bleeding produced by lasing the bone, but charred material and calcium flecks accumulated and were removed by curettement. This resulted in minor bleeding from the bone, easily controlled by cottonoid or gauze pressure. Bleeding from soft tissues was minimal and readily stopped by continued lasing.

The rotation flap was incised with the scalpel and produced the usual brisk bleeding and brightly reddened surfaces contrasting sharply with the relatively dry and brownish black lased areas. The lased area was then easily freshened by wiping away with saline sponges the carbon particles which remained on the surface. This left a more normally colored surface. The lased edges were sutured together, as were the scalpel-cut edges without prior excision of lased tissue and closure was made without tension.

Following operation, the flap maintained good color and circulation. All wound margins healed promptly except for some delay along a 3 cm. segment, where the lased, rotated flap margin had been sutured to the lased ulcer bed margin. However, all margins finally healed completely and sutures were removed by the end of the third week.

The second ulcer, located over the sacrum, was 5 cm. in diameter, round with raised reddened areas and covered by yellowish pus and necrotic material interspersed with gangrenous, blackened tissues. There was also undermining of the edges for 1 cm. on the right side and inferiorly, where a cavity about 1–2 cm. deep, filled with pus and necrotic material, was noted. The operation was carried out on February 28, 1972. Lasing proceeded as for the first operation with part of the sacrum likewise being lased and bleeding was again minimal. One vessel was clamped because it was deep in the undermined area, but with better exposure that vessel was lased after the clamp was removed. The lased edges, but not the base of the ulcer, were, in this case, excised with the scalpel, whereupon bleeding was brisk. This was done because one of us (SW) felt that further evidence was needed to assure healing, before lased edges could safely be sutured together. Closure was done without tension using Hemovac drainage and the ulcer remained healed to the time of discharge 25 days later, on March 23, 1972. Hyperbaric treatment was given as described above. A total of only 56 days of hospitalization was thus needed for treatment of the 2 decubitus ulcers by consecutive operations. At follow-up, 6 months later, both ulcers remained healed.

Case 2. (B.B.) This 42-year-old woman had suffered from multiple sclerosis for 13 or more years. She showed classical signs of the disease, including motor, sensory and visual loss with hyperactive reflexes, positive Babinskis, dysarthria, optic atrophy and urinary incontinence requiring catheterization. Her decubitus ulcer, 2 cm. wide, 6 cm. long and 2–3 cm. deep, was located over the sacrum and had been present for 18 months. She had been bedridden for 6–7 years. Excision and repair of her decubitus ulcer at another institution nearly a year ago had failed. Local and general medical treatment had consisted of the usual applications as well as hormones, hematinics, vitamins, antibiotics and antispasmodics.

The decubitus ulcer was covered by some granulation tissue, but mostly by pus and necrotic material strongly adherent to the base. The skin edges were thickened, raised and reddened. At operation on February 10, 1972, the laser was used first at 10 watts output and gradually raised to 80 watts except for the end stages when it was reduced. The edges, but not the base, of the ulcer were excised with the scalpel, since one of us (S.W.) was again concerned as for the sacral ulcer in Case 1. The technique was otherwise the same as for Case 1, including the flap rotation down to muscle layer and the closure. Figs. 1–4 show the original ulcer, the lesion after cleaning with the laser, the scalpel cut rotation flap and resultant bleeding and, finally, the healed wound. Unfortunately, the black and white photographs do not clearly show the great difference due to bleeding between the relatively dry, lased tissues and the heavily bloody flap resulting as usual from the scalpel incisions.

Case 3. (G.H.) This 78-year-old woman, referred through the courtesy of Dr. Kevin Leen at St. Barnabas Medical Center, had been admitted directly from a nearby nursing home for treatment of a foul-smelling, badly infected bed sore of the left heel. It was reported as being "chronic" and had undoubtedly been present for many months. The patient was suffering from chronic dementia with confusion and disorientation and could

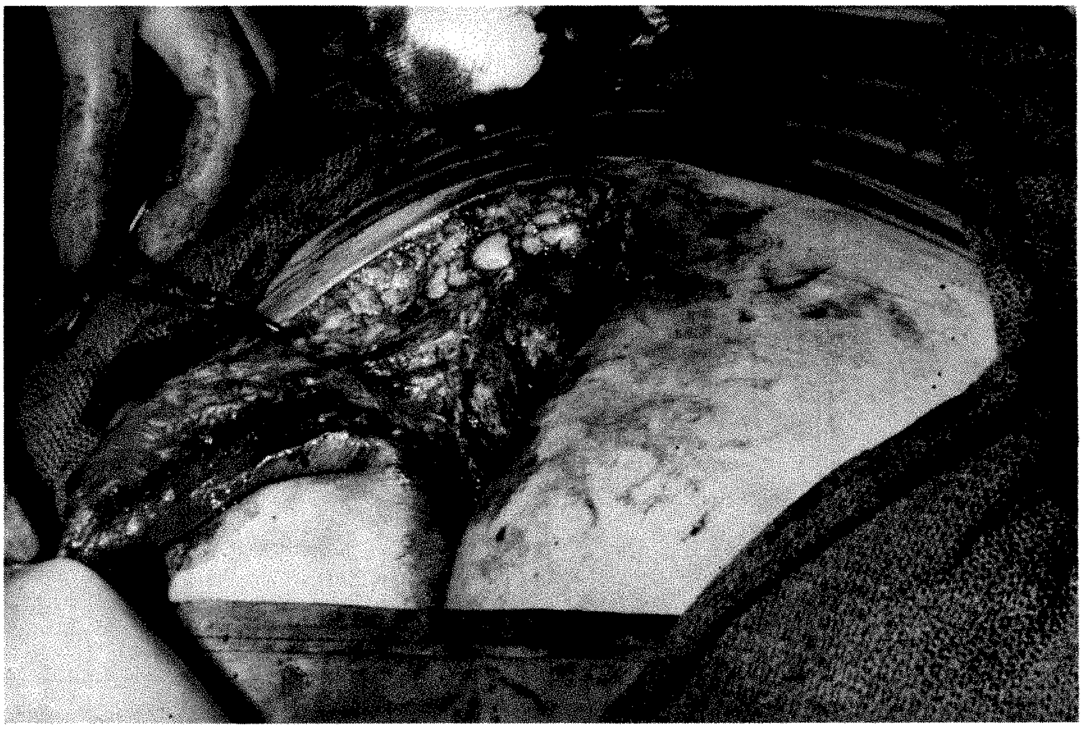

FIG. 3. Same case as Figs. 1 and 2 showing the scalpel-cut flap and scalpel-cut edges of the ulcer with resultant heavy bleeding. (This is much more strikingly seen in the color photograph)

give no history. She had fallen recently and fractured her left hip. The hip had been pinned surgically 2 months earlier.

The decubitus ulcer, measuring some 6 cm. in diameter, covered the entire heel. It was coated by a black, gangrenous eschar beneath which was thick pus and necrotic tissue 3 cm. deep and reaching down to bone (Fig. 5). The foot and leg were swollen. X-rays showed osteomyelitis of the os calcis and osteoporosis of adjacent bones with soft tissue swelling involving the left foot and lower leg. Temperature was 38.8°C and blood cultures showed septicemia with gram negative bacteroides. With antibiotics, temperature reverted to normal and blood cultures became negative.

Operation was carried out on February 17, 1972 and the laser was used at from 25–90 watts of power. The mass of eschar and necrotic tissue was excised in a single piece by using the laser at focus as a surgical knife. A circular incision was first made through the adjacent skin edges and the lesion was undercut in the manner previously employed for burn eschar. The remaining pus and devitalized tissue was then vaporized as in the cases described above. There was virtually no bleeding. Necrotic bone of the os calcis was vaporized by the laser without difficulty. The base appeared to be so clean that the plan previously agreed upon to omit grafting and simply allow the wound to granulate was abandoned. Instead a small, split-thickness, skin graft was taken from the left calf by the disposable Davol Dermatome, meshed and applied to the base of the newly cleaned ulcer. To our surprise, 90% of the graft, estimated grossly, "took" at first but some of it sloughed later leaving an estimated 80% "take." At the time of transfer back to the nursing home 25 days later, on March 13, 1972, the grafted heel was clean and epithelialization had spread further. A follow-up visit 5 months later revealed complete coverage of the heel by healthy-looking skin (Fig. 6). The patient, although still demented, was in reasonably good shape otherwise. This result, in the presence of adjacent osteomyelitis was most gratifying.

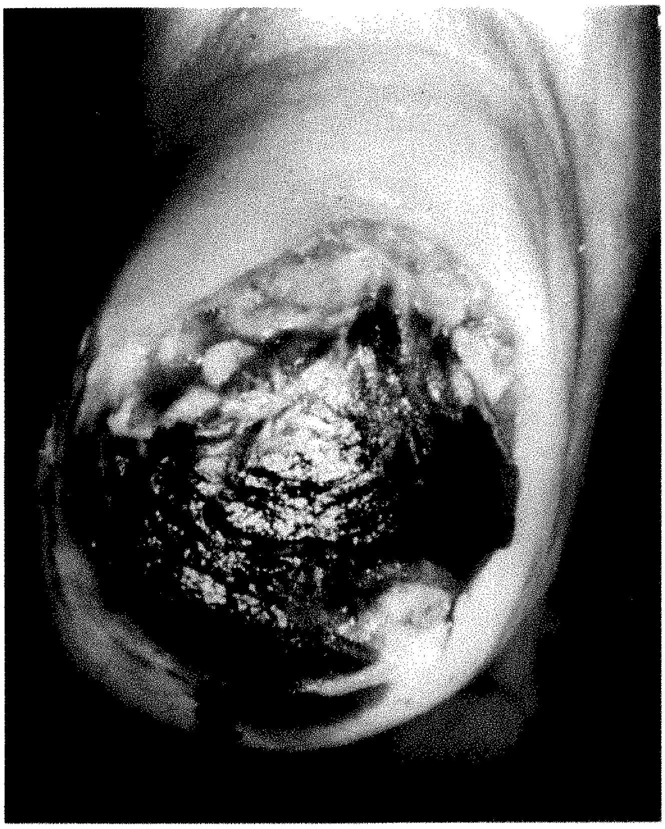
Fig. 5. Ulcer of heel (Case 3, G.H.), before lasing showing black eschar and necrotic covering.

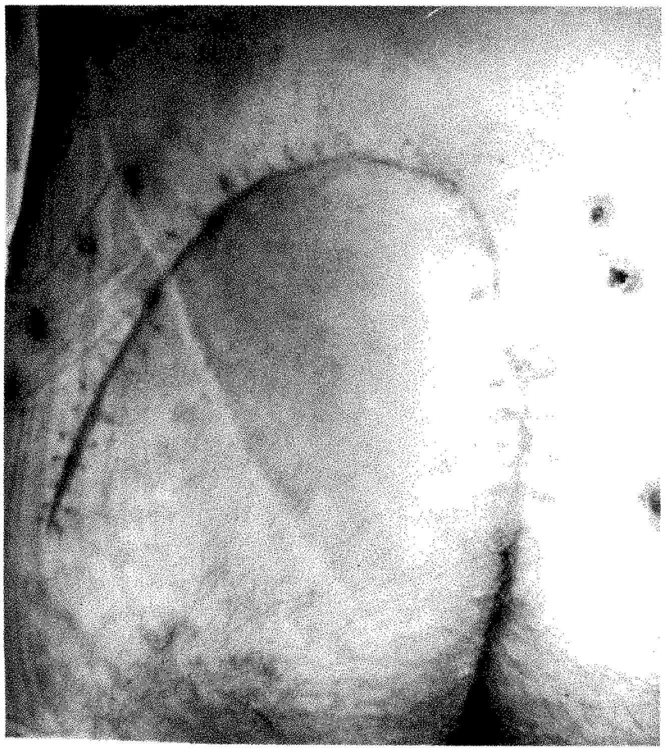
Fig. 4. Same case as Figs. 1, 2 and 3, showing the completely healed wound.

Case 4. (E.Z.) This 49-year-old woman was referred through the courtesy of Dr. Edward Sturchio, Orthopedist, of St. Barnabas Medical Center, who had done a hip-pinning recently for fracture of the right femur. She had suffered from multiple sclerosis for 8 or more years. Neurological examination showed spastic paraparesis with hyperreflexia and bilateral Babinskis, deep sensory loss in the legs, pallor of the optic discs and inability to walk.

The decubitus ulcer, sacral in location, was 4 cm. in diameter and 3 cm. deep. It was covered with pus and necrotic material. The skin edges were reddened and undermined for a distance of 3–5 cm.

Operation was carried out on June 8, 1972 and the undermined skin edges were excised using the laser at focus as a surgical knife. Following that, the dead tissue and pus were vaporized down to a clean base using the laser off focus at high powers (up to 90 watts). The rotation flap was made as usual and lased edges were sutured together without scalpel excision. Hemovac drainage was used. Other details were as given in Cases 1–3. This patient did not receive hyperbaric therapy.

Postoperatively the flap maintained good color and circulation. Wound margins healed promptly except for a 3 cm. long area of delay, where the narrow, rotated portion of the flap was sutured to the lased margin of the ulcer bed. The wound edges there were slightly erythematous and exhibited a 2 mm. wide zone of separation. Moreover, there was mild sero-sanguineous discharge from this region for about 3 weeks, following

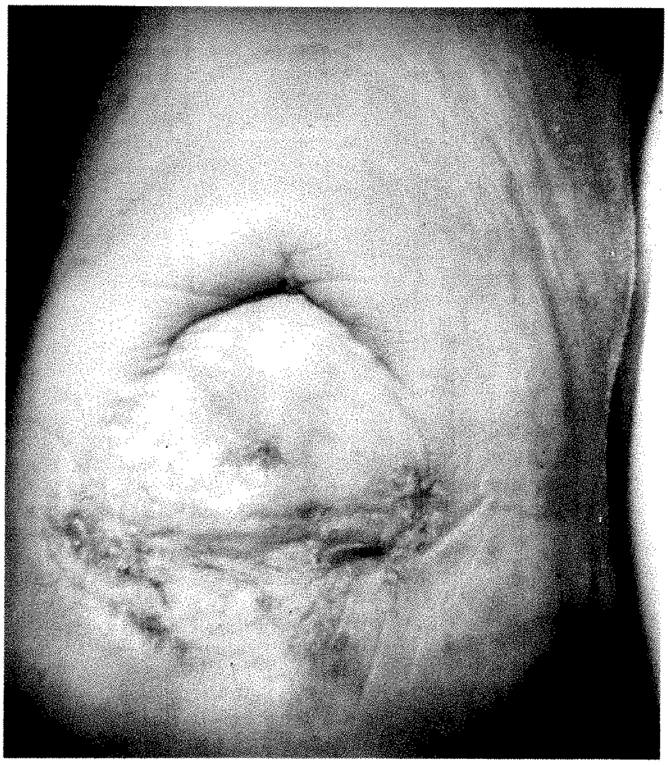

FIG. 6. Same case as Fig. 5, showing complete healing after CO_2 laser debridement and application of meshed skin autograft.

which there was progressive and complete healing. The patient was discharged on July 18, 1972, 41 days after operation.

Results

Carbon dioxide laser debridement of chronic, grossly infected, decubitus ulcers, all recalcitrant to conventional medical therapy and, in one case, to previous surgical treatment by conventional means, resulted in a clean bed which accepted rotation flaps in 4 instances and a mesh, split-thickness skin autograft in one instance. In every case, complete healing took place. In each patient, healing persisted during the follow-up period which varied from 1 to 6 months. An excellent result occurred in the single case of decubitus ulcer of the heel treated by a split thickness graft, despite the presence of underlying osteomyelitis of the os calcis. A total of 5 ulcers in 4 patients were so treated.

Laser debridement was rapid, efficient and complete in previously unprepared lesions. It, therefore, seems evident that when using laser treatment prolonged local and systemic pre-operative care will be unnecessary, if these results are duplicated in our continuing series of bedsore patients. Elapsed days from the time of surgery to discharge after full healing in these 5 ulcers were, 23 (time between the two operations in Case 1), 24, 17, 25 and 41 respectively. These figures are actually a little larger than the time required for healing since some days were always lost in making final disposition after healing was complete.

Hemostatic action of the CO_2 laser in debridement of decubitus ulcers was superb. There was virtually no blood loss. This confirms our previous laboratory experience. The contrast between the lasing of the ulcer bed and the scalpel cutting of the rotation flap was so striking and so vividly shown, as well in the color slides and movies, that there could be no doubt of the laser's superiority to the scalpel in that respect.

Bacteriological studies of the ulcers before, during and immediately after lasing gave encouraging but inconclusive results. As expected, all of the pre-lasing cultures showed organisms. These included staphylococcus epidermidis, coagulase negative, *Proteus vulgaris* or *mirabilis*, citrobacter, *Klebsiella pneumoniae, Escherichia coli,* pseudomonas and *Enterobacter cloacae.*

In 2 of the operations, the post-lasing cultures yielded no growth whatever, showing that *Proteus vulgaris,* Citrobacter, staphylococcus and *Proteus mirabilis* were eliminated. Culture was also negative from one of the specimens taken during lasing but not so from the others. This seems to indicate that lasing must be thorough and complete before bacteriological sterility is achieved. Failure in some of our patients to obtain sterile cultures from the ulcer bed post-lasing may mean simply that, before concluding the surgery, every area must be thoroughly lased and over reliance must not be placed on naked eye observation of apparently healthy tissue. In this way it may be possible even in the worst cases to achieve nearly 100% sterilization.

Histological studies are not yet completed, but preliminary assessment confirms the reports we have given for other tissues showing 1) a layer of charred material dispersed over the surface, 2) a layer of lacunae formation giving a pseudotubular appearance due to evaporation, and 3) a layer of edematous tissue. All 3 layers measure only about 500 microns in thickness. The histological picture, it should be noted will vary with the power input and duration of beam impingement, more intense effects being seen as these are proportionately increased.

Conclusions and Recommendations

1) The carbon dioxide laser rapidly and effectively debrides infected, necrotic decubitus ulcer eschars. 2) Its action is hemostatic, with essentially no blood loss. 3) The resultant lased bed is fully viable and accepts rotation flaps without difficulty. 4) The evidence to date indicates that pre-operative preparation of the ulcer by conventional means is unnecessary. 5) The CO_2 laser gives promise of sterilizing the ulcers.

References

1. Ger, R.: The Surgical Management of Decubitus Ulcers by Muscle Transposition. Surgery, **69**:106, 1971.
2. Griffiths, B. H. and Schultz, R. C.: The Prevention and Surgical Treatment of Recurrent Decubitus Ulcers in Patients with Paraplegia. Plast. Reconstr. Surg., **23**:248, 1961.
3. Hall, R. R., Hill, D. W. and Beach, A. D.: A Carbon Dioxide Laser. Ann. R. Coll. Surg. Engl., **48**:181, 1971.
4. Levine, N., Ger, R., Stellar, S. and Levenson, S.: Use of a Carbon Dioxide Laser for the Debridement of 3rd Degree Burns. Ann. Surg., **179**:118, 1974.
5. Polanyi, T. G., Bredemeier, H. C. and Davis, T.: CO_2 Laser for Surgical Research. J. Med. and Bio. Engl., **8**:541, 1970.
6. Sanchez, S., Eamegdool, S. and Conway, H.: Surgical Treatment of Decubitus Ulcers in Paraplegics. Plast. Reconstr. Surg., **43**:25, 1969.
7. Stellar, S.: Applications of the Carbon Dioxide Laser to Neurosurgical and other Surgical Problems. *In* Proceedings of the IV European Congress of Neurosurgery. Present Limits of Neurosurgery. I. Fusek and Z. Kunc, editors. Avicenum, Czechoslovak Medical Press, Prague, 111, 1972.
8. Stellar, S., Hofstra, P., DeHoff, W. and Crane, S.: Carbon Dioxide Laser Debridement and Successful Immediate Closure of Burn Ulcer Refractory to Treatment in a Dog. (In Preparation).
9. Stellar, S., Levine, N., Ger, R. and Levenson, S.: Carbon Dioxide Laser for Excision of Burn Eschars. Lancet, **945**, 1971.
10. Stellar, S., Levine, N., Ger, R., and Levenson, S.: Laser Excision of Acute 3rd Degree Burns Followed by Immediate Autograft Replacement. J. Trauma., **13**:45, 1973.
11. Stellar, S., Polanyi, T. G. and Bredemeier, H. C.: Experimental Studies with the Carbon Dioxide Laser as a Neurosurgical Instrument. J. Med. and Bio., Engl., **8**:549, 1970.
12. Whitehouse, D. R.: Understanding CO_2 Lasers. Microwave Magazine. Laser Technology Section, **6**:A6, 1967.

The Control of Renal Cortical Perfusion by the Renin Angiotensin System

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THE RATIONALE BEHIND THE PRESENT INVESTIGATION emerges from the experimental and clinical observation that altered renal function and maldistribution of intrarenal blood flow often occur committantly with an altered renin-angiotensin system. Our previous work, using the isolated dog kidney,[1,2] has clearly documented that decreased renal cortical perfusion occurred when one of the components of the renin-angiotensin system, renin substrate, was depleted from the perfusing blood. We proposed that the low plasma renin substrate, which is the precursor for angiotensin formation, resulted in lowered intrarenal generation or angiotensin. It was this lowered level of intrarenal angiotensin that we proposed as being the cause of maldistribution of intrarenal blood flow. The mechanism of this maladaptive syndrome was felt to be related to failure of vasoconstriction in postglomerular vascular beds of the isolated dog kidney. This could conceively cause a progressively greater redistribution of blood flow away from the renal cortex.

A major stimulus for this work has arisen from the recent observation that decreased cortical perfusion and low levels of renin substrate have been measured in cirrhotic patients.[14] These alterations are especially marked when renal function is severely depressed as in the hepatorenal syndrome. It is tempting to postulate that the altered renin-angiotensin system may be etliologically related to the renal malfunction in both the experimental and clinical models. Although these observations are suggestive, the significance of substrate ability, relative to *in vivo* kinetics of the renin-angiotensin system remain to be proven.

In the present work, we have attempted to put this theory on a firmer basis by demonstrating that renin substrate infusions into the substrate depleted isolated kidney can primarily alter the distribution of blood flow to the renal cortex, presumably by augmenting intrarenal angiotensin production. The fact that cortical blood flow is not increased by infusions of angiotensin II, which only causes further cortical vasoconstriction, indicates a significant physiological difference between the actions of intrarenally produced angiotensin II, represented by substrate infusions, and circulating angiotensin II.

Methods

The isolated perfusion circuit comprising a membrane oxygenator, blood pump, heated reservoir, and kidney chamber have previously been described for perfusions using whole blood.[1,2]

A total of 500 ml of blood was used for all perfusions. The initial part of the perfusion lasted 240 minutes and pressure and blood flows were intermittently recorded at 15 min. intervals. Blood flow was measured directly, using a calibrated spout on the venous outflow line of the kidney chamber. Temperatures were maintained at 37°C to obtain optimal physiologic function. Since intrarenal resistance spontaneously decreased during all perfusions, frequent adjustments of flow were necessary to obtain constant perfusion pressure at 120 mm. Hg. Urine was collected at 30 min. intervals and blood was obtained at the midpoint of each collection period for

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the purpose of clearance calculations. The following solution was infused at a rate of 1 ml/min. to partially replace urine volume; creatinine 300 mg%, glucose 150 mg%, NaCl 100 mEq/L. KCl 20 mEq/L, NaH_2PO_4 1.5 mM/L, $CaCl_2$ 1.2 mM/L, sodium lactate 15 mM/L, sodium pyruvate 2 mM/L, and L-proline 10 mM/L. For urine volumes greater than 1 ml/min., NaCl 60 mEq/L was added to the sustaining I.V. to equal urine output. In addition, aldosterone 10 mg/ml and Pitressin (Parke-Davis) 3 mu/ml were infused at a constant rate of .09 ml/min. throughout the entire perfusion. Measurements of plasma and urine creatinine were determined by the method of Bonses.[4] Sodium and potassium were determinded using an Instrumentation Laboratory flame photometer. Osmolality was estimated from freezing point depression by an Osmette osmometer.

After this initial phase of perfusion, one-half of the preparations were infused with purified hog renin-substrate (Pentex Co.) at 625 Ng/min and the other half were infused with angiotensin II (CIBA Hypertensin, asparagine^1-valine^5- angiotensin) at 970 Ng/min. These doses were chosen to give equivalent pressor effects. Infusions were continued for 30 minutes and three 10 min clearance periods were obtained.

Xenon-113 washout curves were obtained initially and then just before and after substrate or angiotensin II infusions. Radioactivity was measured using a 2-inch sodium iodide crystal placed directly over the kidney chamber, connected to a Harshaw digital rate-meter and Teletype printer. The data were then plotted on semi-log paper. The washout curves were analyzed graphically into 2 components and the % distribution to the cortex (% cortex) and cortical blood flow, ml/min/gm cortex, were calculated.

At the end of each perfusion, silicone rubber injections of the microvasculature were obtained by infusion of a low viscosity silastic compound (Microfil, Canton Biomedical products). The compound was allowed to cure overnight at 10°C and then the kidney was cut into 3 mm. thick sections. The tissue was then cleared by dehydrating it in increasing concentrations of ethanol and then methyl salicylate. Sections were examined under a dissecting microscope and photographed at 10 × magnification using high contrast film with an industrial Polaroid camera.

Results

We have previously described the typical pattern of renal function which occurs during isolated kidney perfusion.[1,2] After approximately 120 min. of perfusion, a spontaneous loss of intrarenal resistance has been observed, which resulted in increased renal blood flow since perfusion pressure was maintained constant at 120 mm. Hg.

In Table 1 the average values for renal blood flow observed in 50 recent perfusions are summarized. Renal blood flow per gram kidney (RBF/Gm) initially was 2.8 ± .2 (SEM) ml/min/Gm and remained constant up to 60 min of perfusion time. By 120 min. Flow had approximately doubled, and then increased further to 5.4 ± .3 (SEM) ml/min/Gm at 180 min. The slight drop at 240 min is unexplained, and not felt to be significant compared to the 180 min values. The valve at 240 min is significantly increased over the initial value ($p < .01$).

Sequential measurments of renin and renin substrate also are indicated in Table 1. The method of renin measurement is similar to that described by Gould, *et al.* in humans.[10] It involves incubating excess hog-renin-substrate with each plasma sample to insure that the resultant angiotensin formed is independent of substrate concentration which changes markedly in our preparation. The values for renin are expressed in terms of the amount of nanograms of angiotensin generated per ml of plasma after 18 hours of incubation at 37°C (NgAngio/ml). Although the optimal pH for the human renin hog-renin-substrate reaction is 7.5, we have determined that the optimal pH for dog renin hog-renin-substrate reaction is 6.0. Substrate determinations are made by incubating plasma samples with excess dog renin to insure complete conversion of substrate to angiotensin. Substrate values are expressed as concentration of angiotensin formed after 18 hours of incubation at 37°C

TABLE 1. *Sequential Measurements of Renal Blood Flow, Renin and Renin Substrate during 50 Isolated Kidney Perfusions.*

Perfusion time (min)	0	60	120	180	240
Renal Blood Flow ml/min/gm	2.8 ± .2	2.8 ± .2	4.0 ± .3	5.4 ± .3	4.9 ± .5 $P < .01$
Renin Ng angio/ml	479 ± 55	986 ± 116	2606 ± 395	6824 ± 993	9231 ± 1521
Renin Substrate Ng angio/ml	244 ± 14	229 ± 10	195 ± 11	148 ± 11	106 ± 16 $P < .01$

(NgAngio/ml). The present technique requires only 1 ml of sample and, therefore, multiple determinations are easily performed during each individual experiment. This has allowed us to determine the rate of rise of renin and the decrease in substrate concentration in a sequential manner.

The results indicate that the renin levels increased slowly during the first 60 min of perfusion and then showed a marked increase between 60 and 120 min at the time that RBF increased. The final renin values at 240 min represented a 2000% increase over the initial values. In reciprocal fashion renin substrate levels showed a marked drop from 244 ± 14 (SEM) to 106 ± 16 (SEM) Ng/Angio/ml at 240 min. representing a 57% decrease. Angiotensin formation would be expected to be significantly lower at these reduced substrate levels. To prove this point selected plasma samples were incubated without additional substrate. In these samples 30% less angiotensin was formed in samples removed after 240 min. of perfusion than in control samples removed after 0 or 60 min. of perfusion. This was true despite the fact that renin levels were so much higher in 240 min. samples. This observation emphasized the importance of renin-substrate for angiotensin formation and demonstrated that it was indeed the rate-limiting factor in angiotensin formation in this system.

Table 2 summarizes the pertinent renal functional parameters observed in 18 recent preparations. Only the initial (I) and final (F) clearance periods are given. The initial (I) period was measured over 30 to 60 min. and the final (F) clearance period was measured over 210 to 240 min. It was after this final clearance period that one-half of the preparations were infused with purified hog-renin-substrate and the other half with angiotensin II. These results are shown in Table 3.

From Table 2 it is observed that the direct measurement of renal plasma flow (RPF) approximately doubled with perfusion. However, PAH clearance, C_{PAH}, which is used clinically to measure renal plasma flow, showed essentially no change. The ratio of C_{PAH}/RPF fell from .78 ± .11 (SEM) to .49 ± .06 (SEM). Since PAH is excreted only via the proximal tubules located in the cortex, values of C_{PAH}/RPF should always be less then 1, since some blood always perfuses non-cortical areas. The lower the values of this ratio, the greater the amount of blood perfusing non-glomerular areas. The values that we obtained indicated that a much greater proportion of the total blood flow perfused the noncortical non-glomerular areas during the final, substrate deficient phase of perfusion, than was perfusing it initially.

TABLE 2. *Renal Function of 18 Isolated Kidney Preparations Priro to Infusion*

	Initial (I) 30–60 min Perfusion	Final (F) 210–240 min Perfusion
RPF ml/min	92 ± 8.9*	158.9 ± 13.1
C_{PAH} ml/min	72.3 ± 14	78.1 ± 11
C_{PAH}/RPF	.78 ± .11	.49 ± .06
% Cortex Xenon-133 washout	85.8 ± .7	66.4 ± 2.4
Perfusion Rate Cortex ml/min/Gm Xenon-133 washout	2.7 ± .2	5.7 ± .6
C_{cr}/GM ml/min/Gm	.49 ± .03	.55 ± .04
C_{cr}/RPF	.26 ± .02	.16 ± .01
V ml/min	1.7 ± .2	3.0 ± .6
C_{H_2O} ml/min	−.06 ± .12	+1.50 ± .32
C_{Na}/C_{cr}	.060 ± .005	.048 ± .008

* ±SEM

TABLE 3. *Changes in Renal Function after Infusion of Renin Substrate and Angiotensin II*

	% Change After Substrate Infusion	% Change After Angiotensin Infusion
RPF ml/min	−3.9 ns	−18.8 p < .01
C_{PAH} ml/min	+28.2 p < .01	−36.8 p < .01
C_{PAH}/RPF	+33.3 p < .01	−29.0 p < .01
% Cortex Xenon-133 washout	+16.5 p < .01	−24.8 p < .01
Perfusion rate Cortex ml/min/Gm Xenon-133 washout	−13.5 ns	+14.5 ns
C_{cr}/GM ml/min/Gm	0.0 ns	−10.8 ns
C_{cr}/RPF	+5.9 ns	−5.5 ns
C_{Na}/C_{cr}	+31.8 p < .01	+146 p .01
C_{H_2O} ml/min	+13.3 ns	+115 p < .01
Renin Substrate NgAngio/ml	+7.3 ns	−18.8 p < .01
Renin NgAngio/ml	+6.2 ns	+30.9 ns

More accurate determination of the shifts in intrarenal blood flow were provided by measuring the washout of Xenon-133 from our kidney preparation (Fig. 1). We have previously confirmed the validity of the Xenon-133 washout technique for measuring renal blood flow in the isolated kidney.[6] In the present preparation the percentage of blood flow distributed to the cortex (% cortex) went from initial values of 85.5 ± .7 (SEM)% to 66.4 ± 2.4 (SEM)%, a highly significant difference ($p < .01$), but at the same time the absolute perfusion rate of the cortex went from 2.7 ± 2 (SEM) to 5.7 ± .6 (SEM) ml/min/Gm, approximately double the initial flow value (Table 2). This indicated that the cause of the shift of

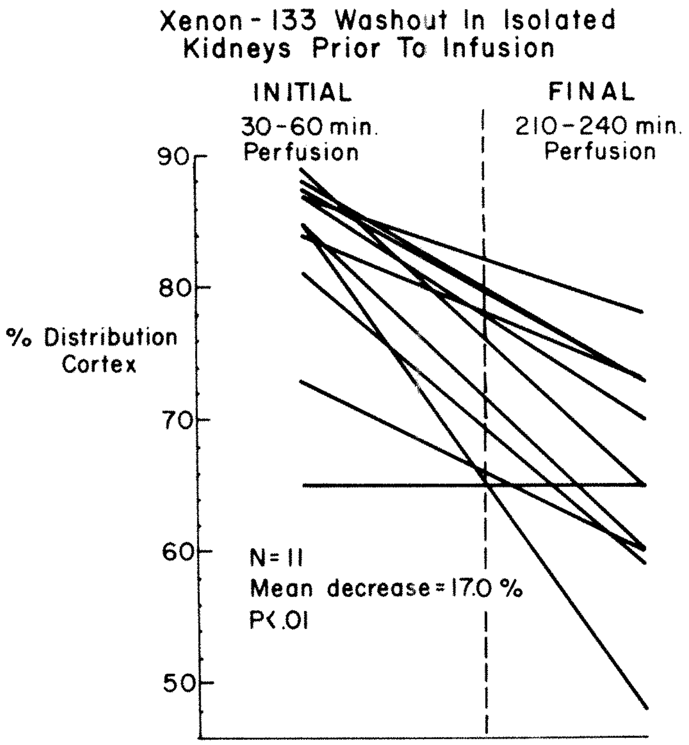


FIG. 1. Distribution of renal blood flow measured by Xenon-133 washout. Effect of perfusion time.

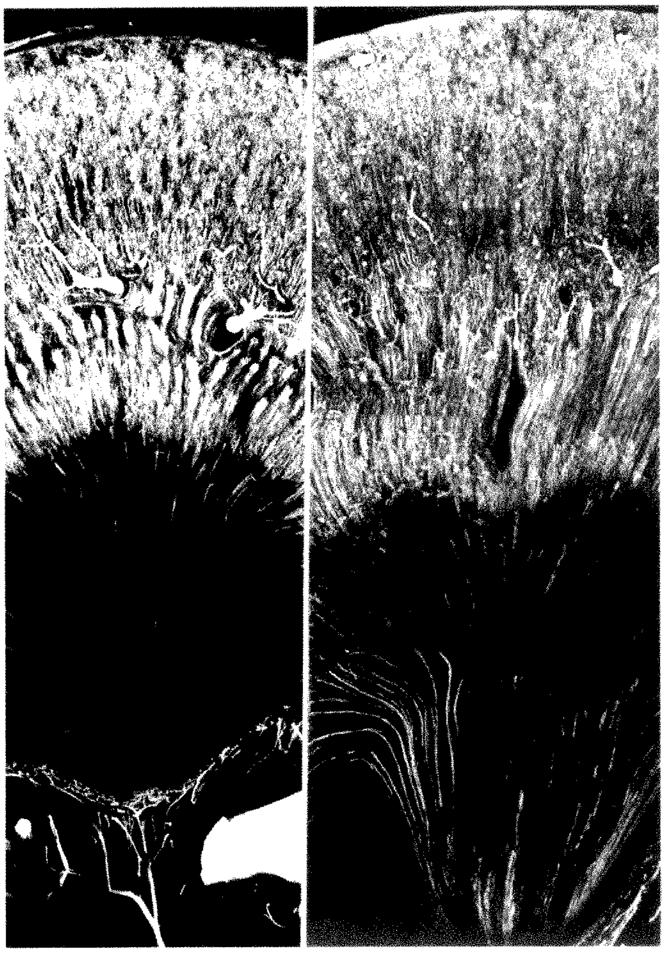
blood flow was not the result of cortical vasoconstriction, but rather a greater vasodilatation had occurred in noncortical vascular beds, such as the medulla, than had occurred in the cortical vascular beds.

This was confirmed, in readily observable form, by using the technique of injecting low viscosity silicone rubber compounds into the isolated kidney. This material hardens and then after appropriate cutting and clearing of the renal tissue gives a detailed picture of the microvasculature of the kidney. In Fig. 2 a comparison of photographs that were taken of a kidney removed in the latter, or substrate-depleted, stage of perfusion (B) is compared with a kidney removed during the time of adequate substrate levels, and more normal renal perfusion at 60 min. A). The greater perfusion of both the cortex and the medulla is clearly shown in the specimen removed and injected after 240 min. of perfusion. The pictures clearly show that there is no evidence for cortical vasoconstriction during the latter stage of perfusion, to explain the relatively decreased % cortical perfusion.

The other parameters of renal function in Table 2 indicated that C_{cr} changed very little with perfusion. Filtration fraction (C_{cr}/RPF), however, fell from .26 ± .02 (SEM) to .16 ± .01 (SEM) mainly due to the increased levels of RPF. This was probably the result of two mechanisms: 1) a major increment of the increased overall blood flow did not perfuse glomeruli-rich areas and, therefore, this increased flow did not contribute anything to increased filtration: 2) vasodilatation in the cortex was equally affected in both postglomerular (efferent) and preglomerular (afferent) arterioles, thus maintaining the same filtration pressure, and therefore, a constant C_{cr} while cortical perfusion rates rose.

Urine volume approximately doubled with perfusion from 1.7 ± .2 (SEM) to 3.0 ± .6 (SEM). A loss of concentrating ability was demonstrated by the free water clearance changing from the negative value of −.06 ± .12 (SEM) to a positive value of +1.50 ± .32 (SEM). This occurred despite continued infusions of pitressin and aldosterone.

The fractional excretion of sodium (C_{Na}/C_{cr}), fell from .060 ± .005 (SEM) to .048 ± .008 (SEM) indi-



A. B.

FIG. 2. Microfil injection of kidney specimens. A. Specimen injected after 60 min. of isolated perfusion. Normal renin substrate, 250 Ng Angio/ml. B. Specimen injected after 240 min. of isolated perfusion. Low renin substrate, 100 Ng Angio/ml.

cating slightly better sodium conservation in the latter stages of perfusion. Actually, the absolute amount of sodium excreted did in fact increase, but since C_{cr} also increased about 10%, fractional excretion was lower.

Having clearly established the pattern of function in the isolated kidney preparation, the next step was to see if renal function could be changed by manipulating the renin-angiotensin system. This was accomplished by infusing purified hog-renin-substrate (Pentex Company) and angiotensin II (Ciba Hypertensin, asparagine^1-valine^5-angiotensin) into the kidney preparation during the substrate-depleted phase. Clearances and renal blood flows were determined over periods of 240 to 270 min. The results of these experiments are shown in Table 3 and Fig. 3.

Renin substrate was infused at the rate of 625 Ng/min. This dose was chosen to produce a mild vasoconstriction. Experience has shown us that at a higher rate of infusion, for example 1200 Ng/min, a marked vasoconstriction response produced cortical ischemia with poor renal function. This was probable caused by excessive production of angiotensin, by the substrate infusion. A pictorial representation of this is shown in Fig. 4, in which a silastic rubber injected specimen of a kidney preparation that was infused with excess renin substrate (C) shows a very poor pattern of corical perfusion compared to the excellent pattern of cortical perfusion in the kidney infused with the lower level of substrate (B). The results of these experiments are expressed as the maximum percent changes from preinfusion control values (Table 3 and Fig. 3). During substrate infusion the actual RPF fell only 3.9% and was not significant. However, both PAH clearance, C_{PAH} and the ratio of C_{PAH} to RPF. C_{PAH}/RPF, increased 28.2 and 33.3% respectively, suggesting that a redistribution of blood flow had occurred to the cortex. The results of the Xenon-133 washout curves confirmed this. The percent distribution to the cortex increased 16.5% which was highly significant ($p < .01$). There was no significant change in absolute perfusion rate of the cortex.

In contrast to these results, the angiotensin which was infused at 970 NgAngio/min decreased RPF but produced a 36.8% drop in C_{PAH} and a 29.0% drop in C_{PAH}/RPF, suggesting that less blood was in fact perfusing the cortex. This was borne out by measurements of Xenon-133 washout curves which showed that cortical perfusion had decreased by 24.8%. These data indicate that intrarenal angiotensin formed by substrate infusion had a significant role in controlling intrarenal hemodynamics. The angiotensin perfusion consistently made blood flow distribution to the cortex worse by all measured parameters, and stressed the importance of intrarenal generation of angiotensin for selective vasoconstriction.

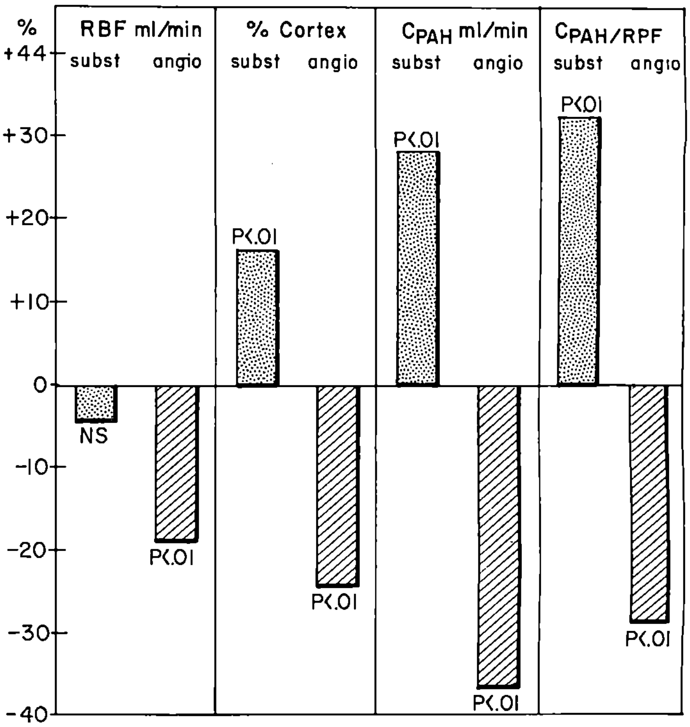
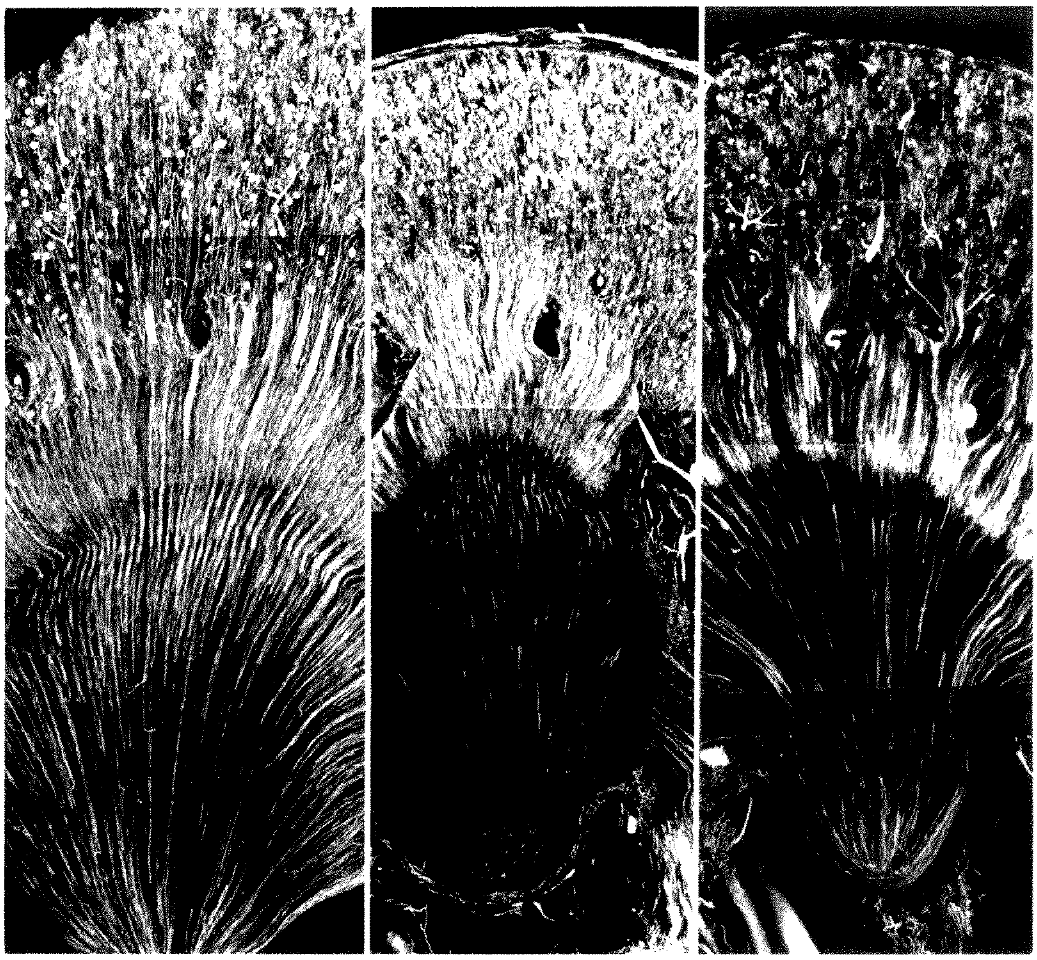


FIG. 3. Per cent change in renal function parameters secondary to infusions of renin substrate and angiotensin II.

Less significant changes were observed in the remaining parameters of renal function Table 3. Creatinine clearance was unchanged and although C_{cr}/RPF increased 5.9% this was not statistically significant, although in all previous experiments it was indeed very rare to see a spontaneous increase in the filtration fraction. Angiotensin infusions resulted in decreased C_{cr}/RPF suggesting that it was causing predominantly preglomerular (afferent) arteriorlar constriction. In contrast to this, the substrate infusions produced a greater effect on postglomerular (efferent) vessels, presumably by the liberation of intrarenal angiotensin.

Angiotensin infusion produced a greater increase in sodium and free water excretion than the substrate infusions. This was probably the result of shifting blood to areas of relatively low sodium reabsorptive capacities.

The measurements of renin substrate verify that a 7.3% increase resulted during substrate infusion. While the calculated infused amount of substrate should have produced a greater elevation of the serum levels, we did not observe this. We are of the opinion that the infused substrate was rapidly converted to angiotensin at intrarenal sites during one pass through the kidney. Itskovitz[12] clearly has demonstrated increased levels of renal venous



A. B. C.

FIG. 4. Microfil injection of kidney specimens after A. Angiotensin infusion, 970 Ng/min. B. Renin substrate infusion, 625 Ng/min. C. Excess renin substrate infusion, 1200 Ng/min.

angiotensin when he infused synthetic renin substrate into a similar isolated kidney preparation. During angiotensin infusion, the levels of renin substrate fell 18.8% due to the continued utilization of renin substrate in our preparation. Renin levels continued to increase slightly during both substrate and angiotensin infusions. Although the rate of increase was less with substrate infusion, the differences were not significant enough to allow speculation concerning a possible negative feedback mechanism, due to the renin substrate infusions.

Discussion

The results of these experiments indicate that the intrarenal production of angiotensin has a significant controlling effect on the amount of blood perfusing the cortex. At first glance it might seem contradictory that similar results were not obtained with angiotensin II infusions. There is, however, ample precedent to support a different physiologic response to angiotensin produced at intrarenal sites and circulating angiotensin II. Carriere,[5] using intact dog kidneys, measured marked decreases in renal cortical perfusion after the infusion of angiotensin II. Glomerular filtration and filtration fraction were also markedly reduced. This suggested that both afferent and efferent arterioles were being vasoconstricted. Infusion of Angiotensin I, which is not vasoactive until acted upon by converting enzyme intrarenally to form angiotensin II, produced only small decreases in cortical perfusion and glomerular filtration remained constant.[6] Filtration fraction actually increased indicating that the site of action of the intrarenally formed angiotensin II was predominantly on efferent arterioles. Franklin[8] demonstrated that about 20% conversion of angiotensin I took place in a single pass through the renovascular bed in the intact dog kidney. We did not measure the actual amount of conversion of renin substrate to angiotensin II in our preparation. Pressure responses, however, could only have been produced by conversion of substrate to angiotensin II since renin substrate is not vasoactive. Using a similar preparation to our own, Itskovitz,[12] actually measured increased levels of angiotensin I and II in the efferent renal venous blood after infusing renin substrate. It would therefore appear that the conversion of renin substrate to angiotensin II can take place at appreciable rates in a single pass through the renal vascular bed.

The clinical correlation of these findings to the hepatorenal syndrome is intriguing. Haynes and Dexter[11] first suggested that an altered renin angiotensin system might be the etiology of this poorly understood renal failure because of the depressed levels of renin substrate observed in these patients. While defective hepatic production was the most likely cause of the altered substrate, increased utilization was also considered to be a factor, since renin levels were often elevated. Our observations, as well as those of others,[14] have indicated that in some cirrhotics, especially those with the poorest renal function and lowest substrate (Table 4) the substrate was the limiting factor for angiotensin formation *in vivo*. The concentration of substrate was so low in some patients that no angiotensin was generated after incubation of the patients' plasma with huge excesses of renin. Only by adding purified renin substrate to these samples could angiotensin formation be detected.

The suggestion that decreased intrarenal angiotensin production may be related to altered renal hemodynamics and/or decreased arteriolar perfusion pressure has been suggested. Recent measurements of intrarenal blood flow in cirrhotic patients,[7,13] using Xenon-133 washout techniques showed significant decreases in cortical perfusion. The lowest values of cortical perfusion correlated with the lowest glomerular filtration rates. Although cortical vasoconstriction could explain these findings, an alternative interpretation is that a relatively greater vasodilitation had occurred in non-cortical or medullary vascular beds. This formulation would suggest that certain vasoconstrictive agents may have a beneficial result on renal function. Indeed, this has been found to be true with at least one pressor agent, Aramine, which has been evaluated by ourselves as well as others.[9,15] Patients who had a beneficial result from Aramine infusions responded with increased urine output, increased renal blood flow, increased creatinine clearances, and return of previously elevated cardiac indexes to normal levels. We would not have expected these improvements in renal function and renal hemodynamics to have occurred if renal cortical vasoconstriction was present.

Since it is apparent that the production of angiotensin is probably reduced in the hepatorenal syndrome because of the low renin substrate levels, this might be the cause of the altered intrarenal vascular resistance. The consistency of these two findings, by ourselves as well as others, has increased our conviction that they are causally related. We feel that the key experiments that remain to be done in this regard must involve the preparation and infusion of purified human renin substrate into patients manifesting the hepatorenal syndrome.

TABLE 4. *Measurement of Plasma Renin and Renin Substrate Cirrhotic Patients. (Renin Results are Expressed as Goldblatt Units/ml (G.U./ml)*[10]

	Plasma Renin G.U./ml × 10^{-4}	Renin Substrate Ng angio/ml
Normal	0–2.0	460–880
Schroeder		
17 Cirrhotics, non azotemic	12.6	235 ± 40
5 Cirrhotics, azotemic	174.0	285 ± 108
Berkowitz		
9 Cirrhotics, azotemic	22.5	266 ± 38

Summary

We feel that the results clearly show that the intrarenal production of angiotensin by administration of hog-renin-substrate has a significant controlling effect on the amount of blood perfusing the cortex. These results seem to have far-reaching significance beyond the isolated kidney. It appears that this is the first time that the renin-angiotensin system has been shown to possess a definite regulatory function in the kidney aside from its well known effect on sodium reabsorption. We feel that this demonstration will serve to inaugurate a new era of investigation into the nature of homeostatic renal function as affected by the renin-angiotensin system. Although the most significant changes that we observed were related to blood distribution, the changes in other parameters of renal function, particularly C_{cr} and C_{cr}/RPF were interesting but not statistically significant. This may be related to the characteristics of the isolated kidney preparation as a test system. We hope that in future work we will be able to choose appropriate models to reveal a significant effect of the renin-angiotensin on the control of these parameters of renal function as well.

Acknowledgments

We wish to acknowledge the excellent technical assistance of Charles Sherrill, Juanita Thomas and Isabel Weiman, and the photographic assistance of Joe Rothrock, Alton Dubrey and Leonard Conway.

Addendum

Since submission of this manuscript, a recent publication by Iwatsuki *et al.* (Recovery From "Hepatorenal Syndrome" After Orthotopic Liver Transplantation. N. Engl. J. Med., 289:1155, 1973) has provided some confirmatory evidence that low renin substrate levels may underlie the renal failure of severe liver disease. Following liver transplantation, renin substrate levels rose significantly and preceded the improvement in renal function by several days.

References

1. Berkowitz, H. D., Miller, L. D. and Itskovitz, H. D.: Renal Function and the Renin Angiotensin System in the Isolated Perfused Kidney. Am. J. Physiol., **213**:928, 1967.
2. Berkowitz, H. D., Miller, L. D., Itskovitz, H. D. and Bovee, K. C.: Renal Function in the Isolated Perfused Kidney. Surg. Gynecol. Obstet., **127**:1257, 1968.
3. Bonses, R. W. and Taussky, H. H.: On the Colorometric Determination of Creatinine by the Jaffe Reaction. J. Biol. Chem., **158**:581, 1945.
4. Bovee, K. C., Berkowitz, H. D. and Miller, L. D.: Comparison of Xenon-133 Washout and Renal Venous Flow on the Isolated Perfused Canine Kidney. Am. J. Vet. Res., **33**:511, 1972.
5. Carriere, S. and Friborg, J.: Intrarenal Blood Flow and PAH Extraction During Angiotensin Infusion. Am. J. Physiol., **217**:1708, 1969.
6. Carriere, S. and Biron, P.: Effect of Angiotensin I on Intrarenal Blood Flow Distribution. Am. J. Physiol., **219**:1642, 1970.
7. Epstein, M., Berk, D. P., Hollenberg, N. K., *et al.*: Renal Failure in the Patient with Cirrhosis. Am. J. Med., **49**:175, 1970.
8. Franklin, W. G., Perch, M. J. and Gilmore, J. P.: Evidence for the Renal Conversion of Angiotensin I in the Dog. Circ. Res., **27**:321, 1970.
9. Gornel, D. L., Lancestremere, R. G., Popper, S., *et al.*: Acute Changes in Renal Excretion of Water and Solute in Patients with Laennec's Cirrhosis, Induced by the Administration of the Pressor Amine, Metaraminal. J. Clin. Invest., **41**:594, 1962.
10. Gould, A. B., Skeggs, L. T. and Kahn, J. R.: Measurement of Renin and Substrate Concentrations in Human Serum. Lab. Invest., **15**:1802, 1966.
11. Haynes, F. W. and Dexter, L.: The Renal Humoral Pressor Mechanism in Man IV: The Hypertensiogen Content of the Plasma of Normal Patients and Patients with Various Diseases. J. Clin. Invest., **24**:78, 1945.
12. Itskovitz, H. D., Odya, C., Shah, A. and Denman, T.: Renal Angiotensin System and Renal Hemodynamics. (Abstr.) Washington, D. C., Am. Soc. Nephrology, 37, 1970.
13. Kew, M. C., Varma, R. R., Williams, H. S. et al: Renal and Intrarenal Blood-Flow in Cirrhosis of the Liver. Lancet, **2**:504, 1971.
14. Schroeder, F. T., Eich, R. H. Smulyan, H., Gould, A. B. and Gabuzdu, G. J.: Plasma Renin Level in Hepatic Cirrhosis. Am. J. Med., **49**:186, 1970.
15. Sugarman, H. J., Berkowitz, H. D., Davidson, D. T. and Miller, L. D.: Treatment of the Hepatorenal Syndrome with Metaraminal. Surg. Forum, **21**:359, 1970.

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Use of a Carbon Dioxide Laser for the Debridement of Third Degree Burns

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EXTENSIVE THIRD DEGREE BURNS are always a very serious injury and often lethal. Much of the resultant morbidity and mortality is due to infection originating in the damaged tissue. The irreparably damaged ischemic skin is highly susceptible to infection and this is compounded by the lowered "defenses" of the severely burned patient. As long as devitalized tissue is present, infection is a threat. For healing to occur and recovery to take place, the burned skin must first separate spontaneously or be removed, the resulting wounds must be grafted, the grafts must take, and the donor sites must heal. Local antibiotic and chemotherapeutic agents have helped reduce infection of the burned tissue but have resulted in slower rates of spontaneous sloughing of devitalized burned tissue, presumably by lessening bacterial enzymatic activity. As long as dead skin is present, as long as the granulating area is unhealed, the possibility of serious infection, local and systemic, exists.

Although local and systemic chemotherapy has lowered deaths from septicemia, the incidence of serious burn wound infection is still high and morbidity still too prolonged. In fact, sepsis is still the major cause of death of patients with extensive deep burns.

Recovery and return of function in these patients is contingent to a large degree on the earliest safe removal of the burn eschar and skin grafting. Because spontaneous sloughing of the deeply burned skin generally requires 21–35 days (depending on the site and type of burn), early surgical excision of the eschar and skin grafting (homografting and autografting) have been advocated. Where feasible, this approach is generally successful; but when the deep burn is extensive, massive excision is a formidable procedure involving prolonged anesthesia and considerable blood loss and replacement, carries its own serious complications, and is uncommonly practiced in that group of patients who could profit most from prompt removal of irreparably damaged skin, *i.e.*, the patients with very extensive deep burns. Accordingly, we have investigated the use of a CO_2 laser[1–5] for the excision of third degree burns, with the view that blood loss can be minimized by this technique, and, at the same time, cause minimal damage to the underlying tissue so that immediate skin grafting can be carried out successfully.

Materials and Methods

The instrument[6,7] used in these experiments is a CO_2 laser with an articulating surgical arm of special design, which makes its use simple and easy. This laser derives

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The carbon dioxide laser used in this study is not to be confused with the ruby laser employed in retinal surgery. The ruby laser delivers visible light energy of 6943 angstrom wave length. Eye structures anterior to the retina are relatively transparent to such radiation and therefore not affected by the beam. The CO_2 laser delivers infrared energy of 106,000 angstrom wave length which is absorbed by all tissues. Most ruby lasers are "pulsed" to deliver short bursts of energy lasting milliseconds. The CO_2 laser has a "continuous wave" output which can produce a constant beam of infrared energy for hours at a time. Such continuous wave output enables one to use the laser as a scalpel in general surgical procedures.

its energy from molecular vibration, translation, and rotation in the CO_2 molecule, with a resulting output of a high intensity, coherent, virtually monochromatic beam in the far infrared region at 10.6 microns. Power output can be varied from 0–40 watts with a Variac control. The laser beam is focused by a system of mirrors in the jointed surgical arm and an output lens in the handpiece. An accessory low power suction pump is used to clear away the smoke. A foot pedal control is used for on and off switching of the laser. The action of the laser at powers currently employed appears largely due to heat, with temperatures at a less than 1 mm. focal spot reaching thousands of degrees Celsius. Because tissue is a poor conductor of laser energy, damage is limited to a narrow zone within microns of the laser beam.

We began with the technique of "laser vaporization." Using this method, the laser was directly focused on the burned tissue, converting it to smoke. Although skin with full-thickness burns could be removed in this fashion, this method was too slow, and injury to the underlying tissue often occurred. Skin grafts immediately applied showed poor "takes."

We then used the laser as a scalpel, a technique we refer to as "laser excision." The laser was first used to incise a rim of tissue completely surrounding the burned area. Then a flap of tissue containing burned skin was dissected free of the underlying tissue, using the laser as a "photo-knife" or scalpel. An effort was made to carry out the excision just underneath the burned skin. Usually this was in the subcutaneous region, but in our larger area excisions, this was performed at the fascial level. The depth of the excision was determined by naked eye evaluation.

Hemostasis was usually automatic and resulted from heat coagulation of the small vessels. A few bleeders were encountered and the majority of these could be controlled by applying the laser beam directly to the bleeding vessel. An occasional larger vessel was clamped and tied.

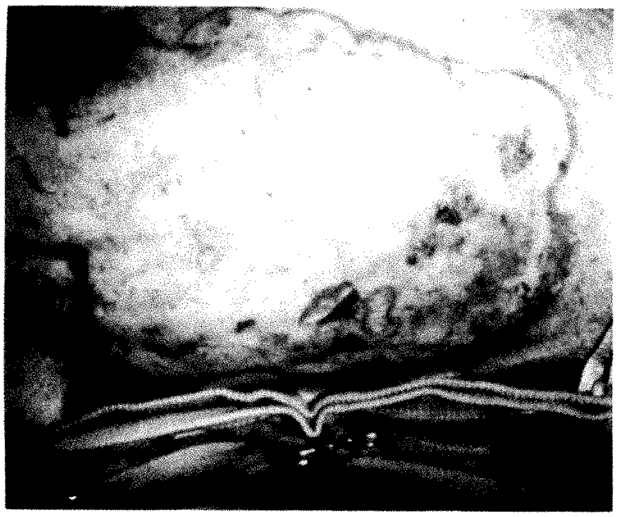

Fig. 1. Pig with large area third degree thermal contact burn, 24 hours post-burn. Photograph taken just before laser excision was performed.

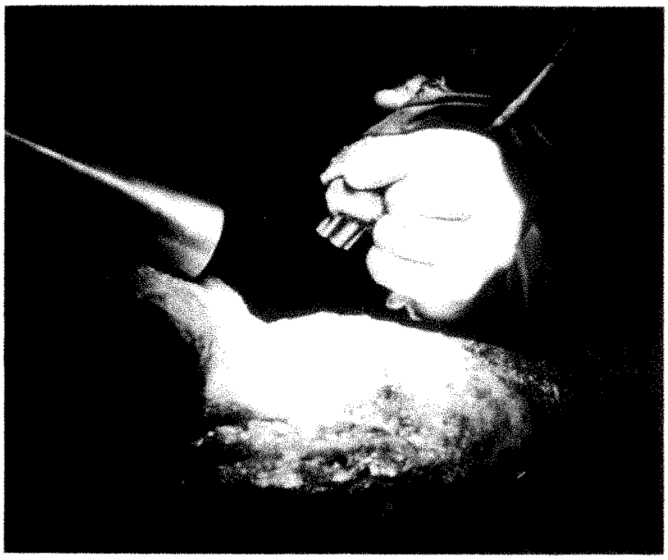

Fig. 2. Carbon dioxide laser being used to excise the third degree pig burn. The handpiece of the carbon dioxide laser is held by the operating surgeon. A vacuum cleaner attachment can also be seen. It is used to clear away the smoke caused by lasing.

The present study employed 3-month-old Hampshire-Landrace pigs weighing from 40–60 lbs. Intravenous pentobarbital anesthesia was administered via a catheter previously placed in the external jugular vein by cutdown. Experimental burns were produced 24 hours prior to lasing in a fashion previously standardized in our laboratory.

Small area burns were produced by thermal contact with a 5 cm. diameter copper cylinder heated to 80°C

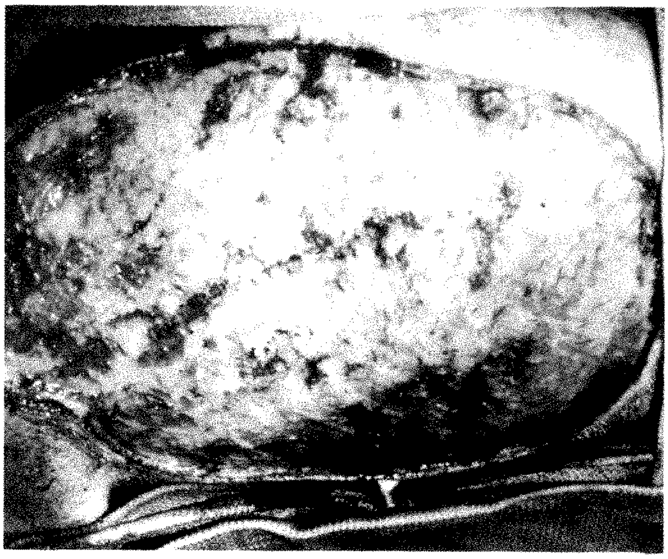

Fig. 3. The same pig immediately following laser excision of the burn. Note that the exposed tissue is healthy looking. Split thickness skin autografts were immediately placed on this area.

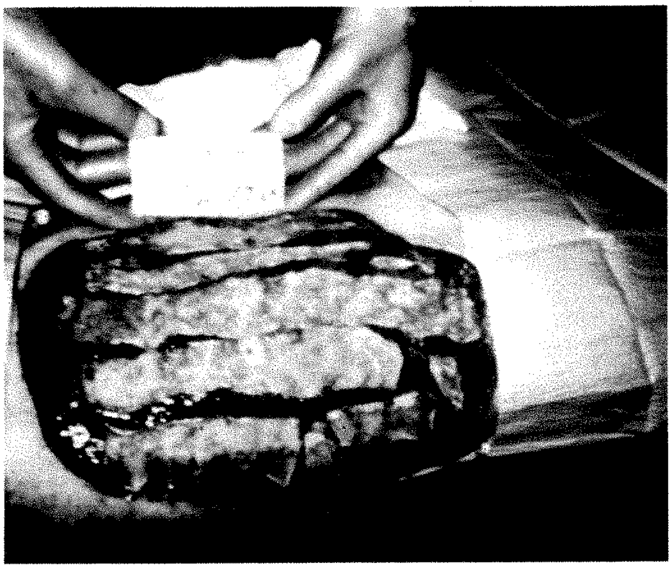

FIG. 4. The same pig 5 days after laser exision and grafting. The grafts have taken. Areas between graft strips have formed red, clean granulation tissue.

and applied for 1 minute and 15 seconds. Large area burns were produced by applying a heat-sealed plastic bag containing water at 80°C for 1 minute and 15 seconds. The plastic pillow was molded to conform to a predetermined area on the side of a pig.

In our initial experiments, 6 pigs with 43 small area burns were used. About half the burns in these pigs were controls, undergoing ordinary surgical scalpel excision with immediate split-thickness skin autografting. The remainder were initially debrided using "laser vaporization." After this technique was abandoned, for the reasons already mentioned, "laser excision" was performed. The larger burns, up to 23 × 28 cm, were then created and tested in a similar fashion, excising the entire burn with the laser and then applying skin autografts.

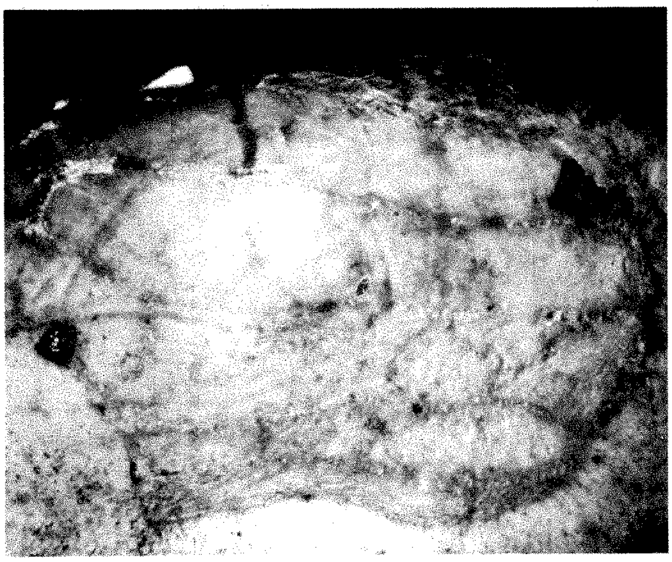

FIG. 5. The same pig 5 weeks after laser exision and grafting. The grafts have persisted in a normal fashion and are beginning to blend with the surrounding tissue.

Following our preliminary studies, a formal comparison of laser versus surgical scalpel excision was performed using 10–15% body surface area burns in pigs of comparable size and weight. In this investigation, 4 pigs were excised with the laser and 5 with the scalpel. Selection of pigs for laser or scalpel excision was randomized. With the exception of one surgical excision, a laser excision and a surgical control were performed on the same day. Because using the laser to vaporize the rim of tissue around the burn was slow, the scalpel was used to circumscribe the burn and the laser used to dissect the base of the burn.

Split thickness skin autografts, 0.020 inches thick, were applied immediately following laser or surgical excision and were secured in place with gauze sponges and a Kerlix gauze roll wrapped circumferentially around the trunk of the pig. The grafts were taken with the Brown electric dermatome.

1000cc of 0.85 M NaCl solution was administered I.V. to each pig on the day of burning and again on the day of grafting. Following this, the pigs were given no intravenous fluids and were allowed free access to food and water.

Blood loss was measured by weighing drapes and sponges before and after the excisions were performed. Because a scalpel was used to circumscribe the burned areas in both the laser and scalpel base excisions, separate measurements of blood loss from the rim and base were made.

Quantitative bacterial cultures from 2 areas (cephalad and caudad) on the base of tissue immediately following laser or scalpel excisions were performed. A sterile 4 square inch gauze pad wet with 0.9% NaCl, was placed on each of the areas above described and left in place for 5 minutes. Each square was then suspended in 25 ml. of sterile trypticase soy broth and shaken gently for 30 minutes at room temperature. One-tenth ml. aliquots were plated on MacConkey and blood agar media and incubated overnight at 37°C. The number of colonies was then multiplied by 10 to give the number of organisms per cm^2 area. In addition, identification of various bacterial species was made.

Hematocrit, WBC, SGOT, SGPT, LDH, and CPK were monitored on each pig on the day of burning, just before excision and grafting and the day after grafting. The serum enzyme studies were repeated at 5 and 10 days post-grafting.

Appearance of the tissue bed following eschar excision and "takes" of the grafts were followed by observation and documented with color photographs.

Results

Our initial experience showed that the tissue beds underlying the burned areas excised with the CO_2 laser looked healthy. Although they were less red than the scalpel excised conrols, graft "takes" were excellent. Three large area burns, each in a different pig, showed 80%, 100% and 100% "takes" respectively. The grafts showed rapid vascularization and remained viable during the period of observation up to 2 months. In a few small area burns in which grafting was deliberately omitted, healthy, clean, red granulations appeared in a few days to a week following escharectomy in both laser and surgically excised burns.

It was apparent from the beginning that blood loss from the laser excisions was markedly less than that from the surgical scalpel controls. One group of 4 laser excised 5 cm. burns was compared for blood loss with 4 scalpel excised controls in the same animal. Seventy grams of blood were lost from the scalpel excisions, while almost no blood was lost from the laser excised burns. This experience was repeated regularly in other animals.

In the large area burns (Table 1) blood loss was calculated in terms of loss per cm^2 of area excised. In 4 large area burns in which the base of the eschar was excised with the laser, blood loss was 0.068 cc/cm.^{2} This was roughly 30% of the blood loss encountered in surgical scalpel excisions of comparable size, 0.217 cc/cm.^{2} Calculations of blood loss per cm^2 for the knife excisions of the rim in comparably sized areas were, of course, similar in both the laser base excisions and the scalpel base excision: 1.36 cc/cm. perimeter in the laser group and 1.32 cc/cm. perimeter in the scalpel group.

The time required for the laser excisions was significantly longer—73 minutes per 15% BSA burn—than that required for the scalpel excision—18 minutes (Table 2). Investigations in progress suggest that the speed of lasing can be significantly increased by using a shorter focal length handpiece, thereby achieving a greater power density at focus. Preliminary work in the laboratory of one of the authors (S.S.) using a CO_2 laser with 2½ times the power of our machine,* suggests that the time required for lasing may be reduced to equal that of scalpel incisions.

Our own experimentation in pigs indicates that using the "cutting" cautery (Liebel-Flarsheim Co.) reduces blood loss and is compatible with graft "take" on the freshly cauterized base. Blood loss with the cautery was roughly 45% of that with scalpel excisions. A direct comparison of laser and cautery excisions has not yet been performed.

TABLE 1. *Laser Excisions with Scalpel Incision of Circumference of Burn*

Pig	Excision (cm.^{2})	%BSA	Blood Loss-Base cc/cm^2	Graft Take
A	877	15%	0.101	100%
C	1050	15%	0.062	100%
E	1070	15%	0.029	90%
G	300	5%	0.080	100%
			Mean 0.068	
Surgical Scalpel Excisions ($p < 0.01$)				
B	880	15%	0.312	100%
D	1062	15%	0.112	100%
F	965	15%	0.222	100%
H	314	5%	0.175	100%
J	315	5%	0.266	100%
			Mean 0.217	
Laser Excisions of Entire Burn				
PB-5	414	not calculated	not calculated	100%
PB-6	530			90%
PB-7	644			100%

Quantitative cultures of the freshly lased bases showed no significant difference in bacterial types or numbers from the surgically excised bases. Staphylococci, Klebsiella, and Proteus were the predominant species found and they varied in number from 0 to 10^3 organisms/cc.

Hematocrits were obtained from the pigs before burning, after burning and one day following laser or scalpel excision. Hematocrits fell in both groups following excision (Table 3). Although the hematocrit decrease in the scalpel excised pigs was more pronounced (20%) than in the laser excised pigs (12%), this difference was not statistically significant.

Serum enzyme values for SGOT, SGPT, LDH and CPK were obtained before burning at 24 hours post-burn (immediately before escharectomy), 24 hours post-escharectomy and grafting, and at 5 and 10 days post-operatively. The mean values for these enzymes rose sharply 24 hours post-burn (Table 4). All enzymatic values decreased almost to normal 24 hours following laser or scalpel excision and remained near pre-burn levels for the next 9 days of observation. There were no statistically significant differences among the enzyme values for laser excised or scalpel excised pigs at the times during which these enzymes were measured.

TABLE 2. *Operative Time for Excisions of 15% BSA Burns*

	Laser	Scalpel
	105 min.	15 min.
	55 min.	25 min.
	60 min.	20 min.
Average	73 min.	18 min.

---

* Designed by Dr. Thomas Polanyi and Mr. Herbert Bredemeier of American Optical Corporation, Framingham, Mass.

TABLE 3. *Mean Hematocrit Values for 4 Laser Excised Pigs Compared to 4 Surgically Excised Pigs*

	Before Burning	24 Hours Post Burn (Before Excision)	48 Hours Post Burn (24 hrs. Post Excision)
Scalpel excision	30.0	26.0	20.3
	(29–34)*	(20–30)	(15–23)
Laser excision	26.0	26.5	23.0
	(18–37)	(24–27)	(22–25)

* Figures in parentheses indicate range of values.

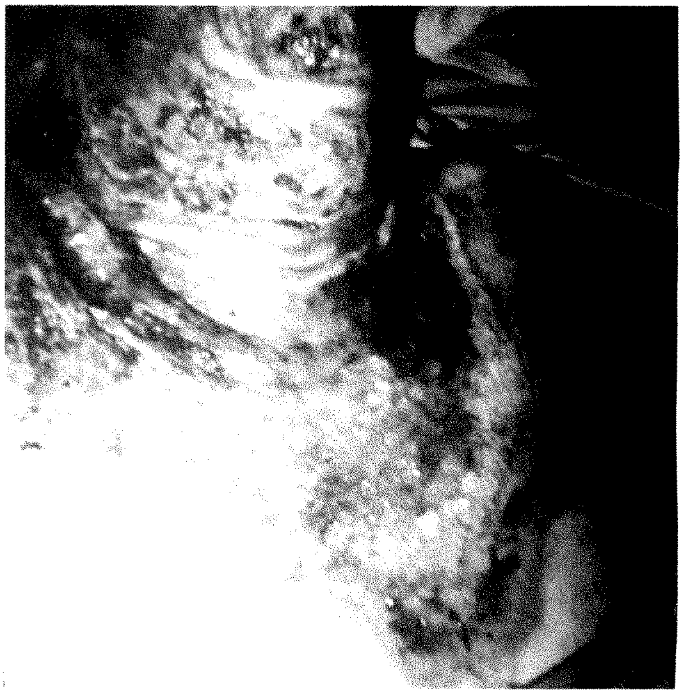

FIG. 6. 72-year-old female, 14 days after incurring a third degree flame burn to neck, shoulders, and upper chest.

The laser excisions proved to be surprisingly feasible from the technical and surgical standpoint. With increasing experience the excision was more swiftly and more efficiently performed. This still was relatively slow, however, using our laser with 40 watts maximum output. There was no problem in protecting the eyes or other parts of the personnel and no difficulty in confining the beam to the burn area desired. Simple caution in aiming the laser sufficed to guard completely against accidental ignition of flammable materials.

Graft takes in all but one of the laser excisions was 100%. In one animal, graft "take" was 90% because of a bunching of the graft in the dressing. All surgical controls showed 100% "takes."

There were no unexpected local or systemic toxic effects from lasing observed in any of the animals.

Because of our favorable results with experimental animals, we have begun a limited trial in patients with burns. To date, laser excision has been performed on one patient. This patient is a 72-year-old female with a symmetrical third degree burn of the neck, shoulders and upper chest (Fig. 6). A decision had been made by the Chief of the Burn Service (Dr. John Stein) to perform a surgical excision of the burn at day 14 post-burn. We obtained permission to perform a laser excision on the left side of the burn and a surgical excision on the right side; the areas to be excised were similar in size and depth. Both excisions proceeded very well. Because the subcutaneous tissue was more vascular in the patient than in our experimental animals, the laser excision required less time and was accompanied by much less bleeding than the surgical excision. The underlying tissue was clean and judged suitable for grafting in both instances (Fig. 7). There was minimal injury to the underlying tissue or to the undersurface of the eschar (Fig. 8). Split thickness mesh autografts immediately applied to the freshly lased and excised surfaces (Fig. 9) showed comparable "takes" (Fig. 10). These grafts have persisted in a normal fashion.

Discussion

Excision of burn slough, by whatever means, must damage the underlying tissue as little as possible. The critical test of the condition of the tissue at the base of the wound is its ability to accept an immediately applied skin autograft. In pigs undergoing laser ex-

TABLE 4. *Mean Serum Enzyme Values Four for Laser Excised Pigs Compared to Five Surgically Excised Pigs*

	Before Burning		24 hrs. Post-Burn (before excision)		48 hrs. Post-Burn (24 hrs. post-excision)		5 days Post-Excision		10 days Post-Excision	
	Laser	Scalpel	Laser	Scalpel	Laser	Scalpel	Laser	Scalpel	Laser	Scalpel
SGOT*	28	23	46	45	24	22	14	17	22	22
	(16–46)	(20–26)	(22–68)	(38–52)	(18–36)	(12–42)	(8–20)	(8–40)	(16–26)	(6–40)
SGRT*	35	26	51	46	45	30	26	20	29	20
	(30–40)	(20–34)	(42–60)	(32–70)	(26–70)	(18–42)	(18–30)	(16–24)	(26–32)	(18–28)
LDH*	670	680	810	780	700	590	580	660	680	600
	(450–780)	(510–890)	(610–1110)	(540–970)	(450–1020)	(430–1000)	(450–750)	(210–1100)	(500–890)	(330–760)
CPK*	30	16	>37	>35	26	20	14	12	23	15
	(9–44)	(8–29)	(19–>40)	(7–>40)	(20–32)	(13–27)	(7–23)	(6–18)	(10–45)	(5–27)

Figures in parentheses indicate range of values.
* Values expressed in units per ml.

cisions of large third degree burns, the "takes" of immediately applied autografts (0.020 inches thick) have ranged from 90–100%. The grafts have vascularized promptly and have persisted intact during the 2 months of observation post-operatively. Blood loss with laser excisions was significantly less than with surgical excisions. So far we have seen no gross evidence of systemic toxicity due to our use of the laser in removing burn eschars of up to 15% total body surface area of the pigs.

Laser radiation has been studied in the skin of man[2] for low energy densities to energy densities as high as 20,000 joules/cm.[2] Our experiments with the large area excisions have involved using the CO_2 laser at 40 watts deliverance for up to 1½ hours. This involves the delivery of an average energy of 335 joules per square cm.[2] which is less than the reported values.

Because of the known carcinogenesis produced by gamma radiation, there has been cause to speculate about laser-induced carcinogenesis in man and experimental animals. To date, there is no evidence to demonstrate experimental carcinogenesis following laser irradiation. Granted, there is a paucity of human investigation with the CO_2 laser. Goldman,[2] however, has studied both humans and animals for over 5 years following laser exposure and found no evidence for the development of malignancy. Histologic studies reveal that the only changes are those of a non-specific fibrosis associated with chronic radiation effects. Thus far there is no evidence to support laser induced carcinogenesis in animals or in man.

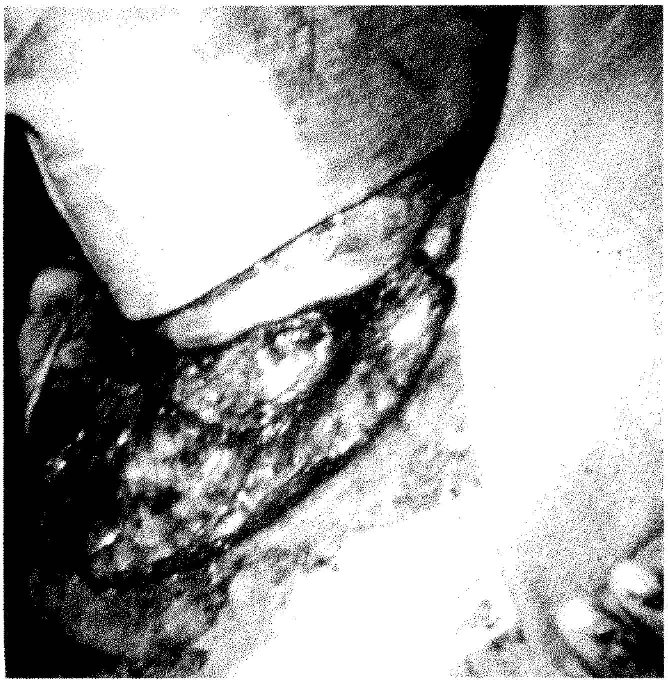

FIG. 7. The same patient after laser and surgical escharectomies of symmetrical areas of the burn. The laser was used to excise the patient's left half (viewer's right); the scalpel was used to excise the patient's right half (viewer's left). Blood loss was less during the laser excision. Minimal damage to the underlying tissue is present.

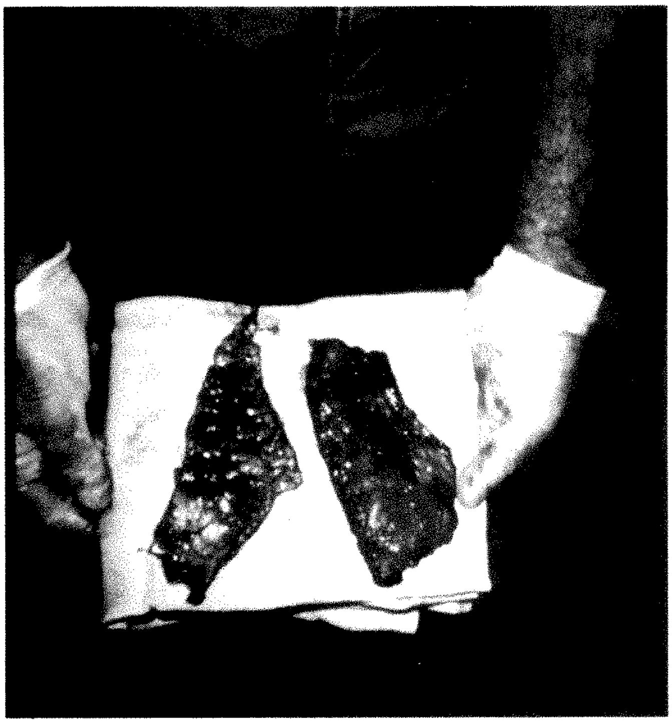

FIG. 8. Undersurface of eschars following laser (right) and scalpel (left) excisions. Note that the undersurface of both specimens shows very little injury to the tissue. Both areas are comparable in size and depth of burn.

The principal disadvantage encountered in using the laser was the slow speed at which the laser excisions were performed. The speed of lasing is determined by

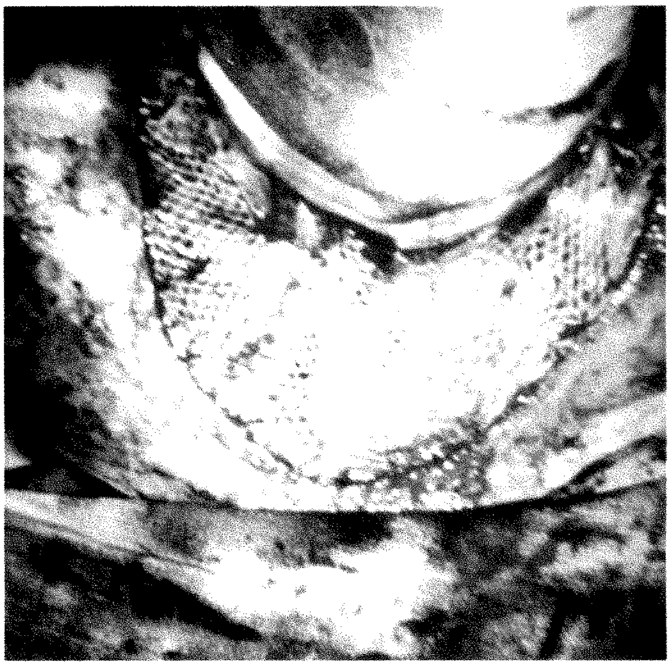

FIG. 9. Split thickness mesh autografts applied to patient immediately after laser and scalpel excisions.

the power density at focus. The power density can be increased in 2 ways. First, the power of the laser can be increased. Second, the focal length of the handpiece can be shortened, with the resulting power density increasing in inverse proportion to the square of the focal length. Preliminary investigations using a CO_2 laser with 2½ times the power of our machine and a short (2 cm.) focal length handpiece indicate that the speed of lasing need be no longer than that required for surgical excision.

Protection for the eyes of personnel against reflected radiation is provided when ordinary corrective lenses or plain glass spectacles are worn. Direct exposure of the hands and the arms of the surgeon to the focused laser beam would result in a burn and must be avoided. Our laser beam, however, is sharply focused within centimeters from the handpiece. This allows for ease of control. With proper skill, the hazards of using a laser should be no greater than those of using the electrocautery.

To date, laser excision of a modest size deep burn in one patient has been carried out, with immediate application of a split-thickness autograft. This was compared with a scalpel excision of a comparable area in the same patient carried out during the same operaton. As in the pigs, blood loss was much less in the area excised with the laser and the "takes" of the skin grafts were similar in both areas.

The CO_2 laser appears to hold substantial promise for the excision of third degree burns in patients. The laser with its special articulating arm is easy to use, the blood loss is much less than that of ordinary surgical excisions, and there is no evidence of local or systemic damage. Skin grafts can be applied immediately after the excisions with essentially complete "takes" resulting. A theoretical advantage of the laser over ordinary scalpel excisions is that the laser seals off small blood vessels and lymphatics and kills microorganisms at the line of excision, factors which should help in minimizing the bacteremia that often occurs following surgical scalpel excisions of deep burns.

Our studies of patients with burns are continuing.

Summary

1) The CO_2 laser has been used for the excision of third degree burns in pigs, with a significant reduction in blood loss when compared to cold-knife excisions of comparable areas.

2) Autografts applied to a freshly lased surface show excellent "takes" and persist in a normal fashion.

3) We have thus far seen no evidence of local or systemic toxicity due to our use of the laser in removing burn eschars of up to 15% body surface area.

4) Our experience with one patient again demonstrated a reduction in blood loss when the laser was used to excise a third degree burn compared to a cold-knife excision of a symmetrical burn. Because the subcutaneous tissue in this patient was much more vascular than that of our experimental animals, scalpel excision required more time than did the laser excision. The "take" of a skin graft immediately applied on the freshly lased surface was comparable to that obtained on the surgically excised area.

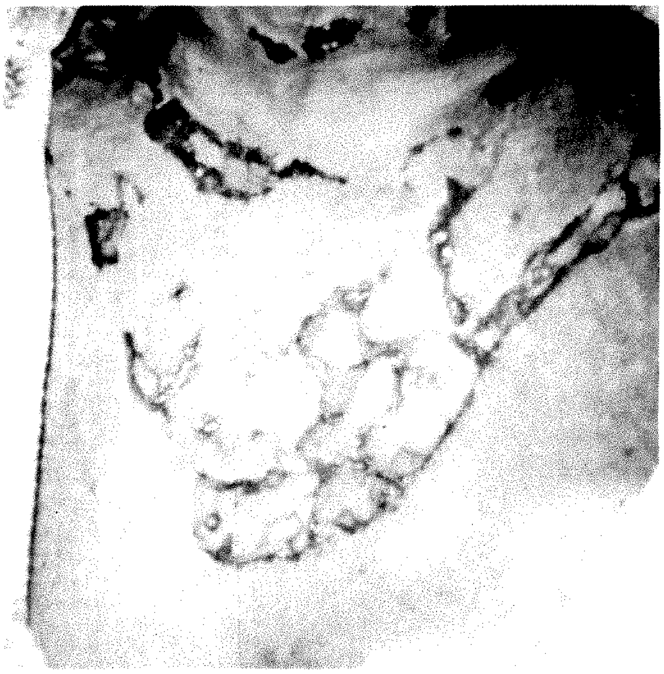

FIG. 10. Same patient, 3 weeks post-grafting. Comparable takes were obtained on both the laser and scalpel excised areas. These grafts have persisted in a normal fashion.

Acknowledgment

We are indebted to Dr. Thomas G. Polanyi and Mr. Herbert C. Bredemeier, physicists of the American Optical Corporation Research Laboratory, Framingham, Mass., who devised, built and loaned the CO_2 laser to us for our investigations. Detailed descriptions of the instrument have been published elsewhere.[6,7]

References

1. Fishlock, D. (ed.): A Guide to the Laser. New York, American Elsevier, 1966.
2. Goldman, L. (ed.): Biomedical Aspects of the Laser. New York, Springer-Verlag, 1967.
3. Goldman, L. (ed.): Second Conference on the Laser. Ann. N.Y. Acad. Sci., **168**:383, 1970.
4. Lengyel, B. A. (ed.): Lasers—Generations of Light by Stimulated Emission. New York, John Wiley & Sons, 1962.
5. McGuff, P. E.: Surgical Applications of Laser. Charles C. Thomas, 1966.
6. Stellar, S., Levine, N., Ger, R. and Levenson, S. M.: Laser Excision of Acute Third Degree Burns Followed by Immediate Autograft Replacement: An Experimental Study in the Pig. (Accepted for publication by J. Trauma).
7. Stellar, S., Polanyi, T. G. and Bredemeier, H. C.: Experimental Studies with the Carbon Dioxide Laser as a Neurosurgical Instrument. Med. Biol. Eng., **8**:549, 1970.

Welcome to the New Chairman of the Editorial Board

It is rare that a person relinquishing a chairmanship has the good fortune to see the man of his choice succeed him. Since this indeed has occurred in this instance, it is a particular pleasure for me to record a note of welcome to Dr. Davis C. Sabiston, Jr., the new Chairman of the Editorial Board of the ANNALS OF SURGERY.

Dr. Sabiston is a North Carolinian. He was born in Onslow County, North Carolina, and attended the University of North Carolina where he received his bachelor's degree. Since 1964, he has served as Professor of Surgery and Chairman of the Department at the Duke University School of Medicine in Durham. He received his medical degree from Johns Hopkins in 1947 and served six years as a House Officer at the Johns Hopkins Hospital, completing the chief residency in surgery in 1953 under Dr. Alfred Blalock. He served successively as Assistant Professor, Associate Professor, and Professor of Surgery at Johns Hopkins School of Medicine, and received a Fulbright Research Scholarship at Oxford in 1960. In 1961, he worked as Research Associate at the Hospital for Sick Children in London. He is a recipient of a Career Research Award from the National Institutes of Health. He is a member of the Society of University Surgeons, The American College of Surgeons, The Southern Surgical Association, The American Surgical Association, The American Association of Thoracic Surgery, The Society for Clinical Surgery, The International Cardiovascular Society, The Society for Vascular Surgery, The Halsted Society, The Surgery Biology Club, The Society for Thoracic Surgery, The Society for Surgery of the Alimentary Tract, and The Society of Thoracic Surgeons of Great Britain and Ireland.

He has been a member of the Editorial Board of the ANNALS OF SURGERY since 1966. He is also a member of the Editorial Board of the Journal of Cardiovascular and Thoracic Surgery; of Circulation; and Editor of the Cardiovascular Surgery Section in Dean Lewis' loose-leaf series *Practice of Surgery.* He is widely known too as Editor of the Davis-Christopher *Textbook of Surgery: The Biological Basis of Modern Surgical Practice.*

ANNALS OF SURGERY, the oldest continuously published surgical journal in the English language, was founded in 1885, starting when the surgical profession was much smaller. It has continued to grow over the years with the profession, and its circulation has increased in almost every year since Dr. Walter E. Lee became Editor in 1935. Its growth rate has increased still further in recent years, and the circulation is now over 17,000. The ANNALS OF SURGERY is the oldest of the 20 medical journals published by the J. B. Lippincott Company, a medical publisher whose lineage goes back to the founding of its earliest component in 1792.

With the election of Dr. Sabiston by the Editorial Board, we have a man ideally prepared by training and experience to serve as the principal Editor of the ANNALS OF SURGERY, and it is indeed a special pleasure to welcome him on behalf of the publisher and the Editorial Board.

JONATHAN E. RHOADS, M.D.

In Deep Appreciation

The Editorial Board of ANNALS OF SURGERY is unanimous in its conviction that Dr. Jonathan E. Rhoads has provided exceptional leadership during his tenure as Chairman. During this period, the journal has experienced an upward trend in its circulation and in its influence upon clinical and investigative surgery in this country and abroad.

Quiet and unassuming in manner, Jonathan Rhoads is an amazing individual whose multiple achievements continue to win the respect and admiration of his colleagues. His ability to provide the highest quality of leadership has been long apparent. From college days at Haverford, where he was Phi Beta Kappa, it was evident that he was a scholar. An outstanding student at Hopkins, where he was elected into Alpha Omega Alpha, he then entered the surgical training program at the University of Pennsylvania. He has since had the ability to speak authoritatively for surgery. His abilities as an Editor are doubtless related to his reputation as a teacher and writer. In original research, his contributions in the field of surgical metabolism are recognized throughout the world. As John Rhea Barton Professor and Chairman of the Department of Surgery at the University of Pennsylvania, he built a strong clinical and research program, and his residents and trainees now hold a variety of important positions as contributors to clinical and investigative surgery.

Few men in American surgery have attained the array of honors which have been accorded Jonathan Rhoads. Moreover, there are numerous tangible results associated with his tenure as Chairman of the Board of Regents of the American College of Surgeons and as President of numerous leading societies including the Philadelphia Academy of Surgery, the Philadelphia College of Physicians, the International Surgical Group, the Society of Surgical Chairmen, the American Cancer Society, the Council of Academic Societies, the Society of Surgery of the Alimentary Tract, the Society of Clinical Surgery, the American Surgical Association, and the American College of Surgeons. He has also been accorded the rare honor of being chosen for membership in the highly selective American Philosophical Society, of which he has also served as an officer. Most recently his major contributions have been in the field of malignant disease, serving as Chairman of the National Cancer Advisory Board and as Editor of the journal of CANCER.

While the many honors and achievements which he has attained speak for themselves, his friends and colleagues recognize that his most important features are those intangible aspects of his breadth of character, sensitivity, courage, and dedication to principle, all of which combine to make him an exemplary scholar and gentleman.

The members of the Editorial Board join in a unanimous note of deep appreciation to a dedicated leader who we are most pleased will remain an active member of the Board and whose wise counsel and advice will continue to be sought in the future.

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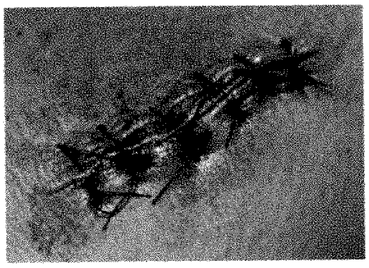

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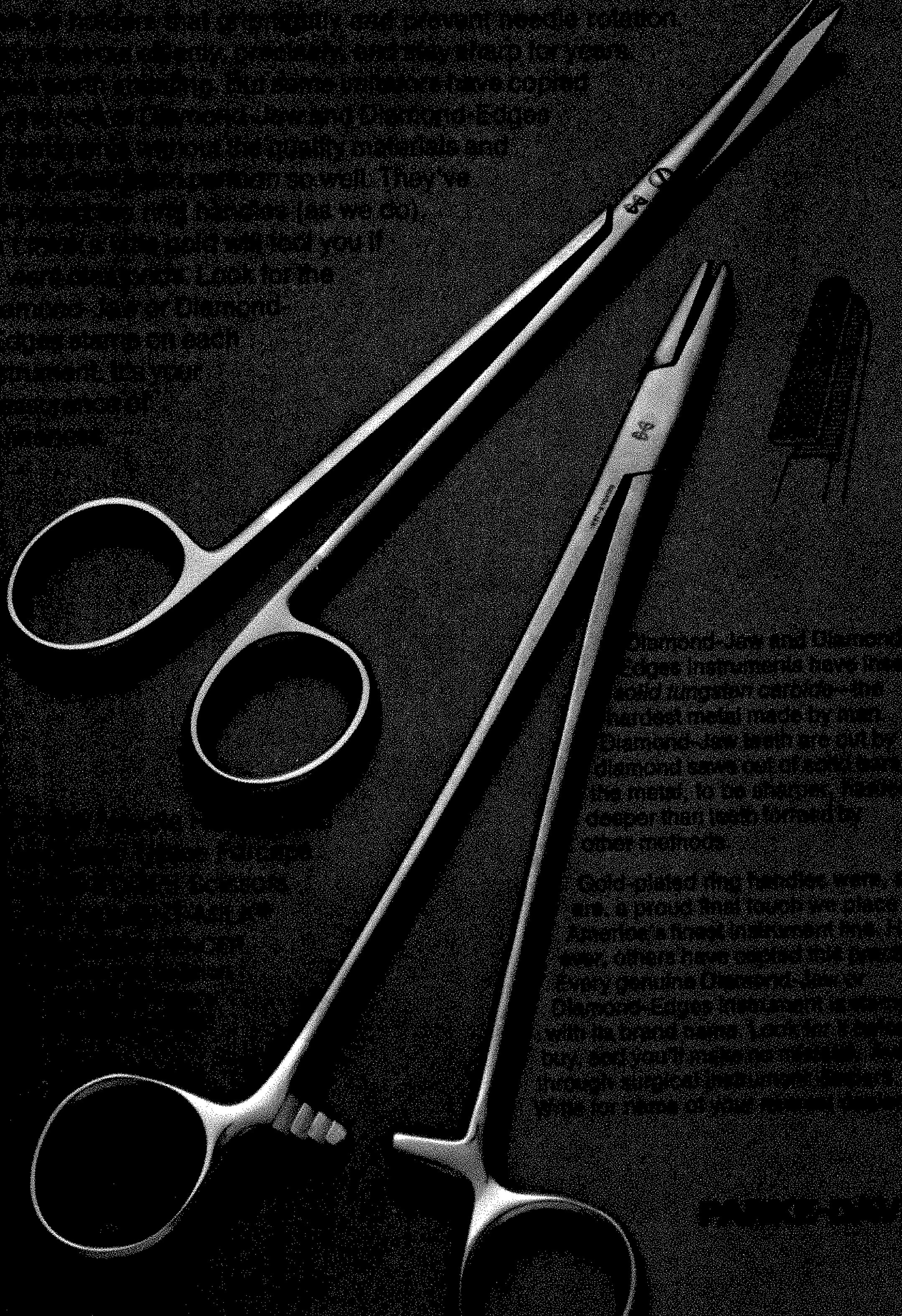

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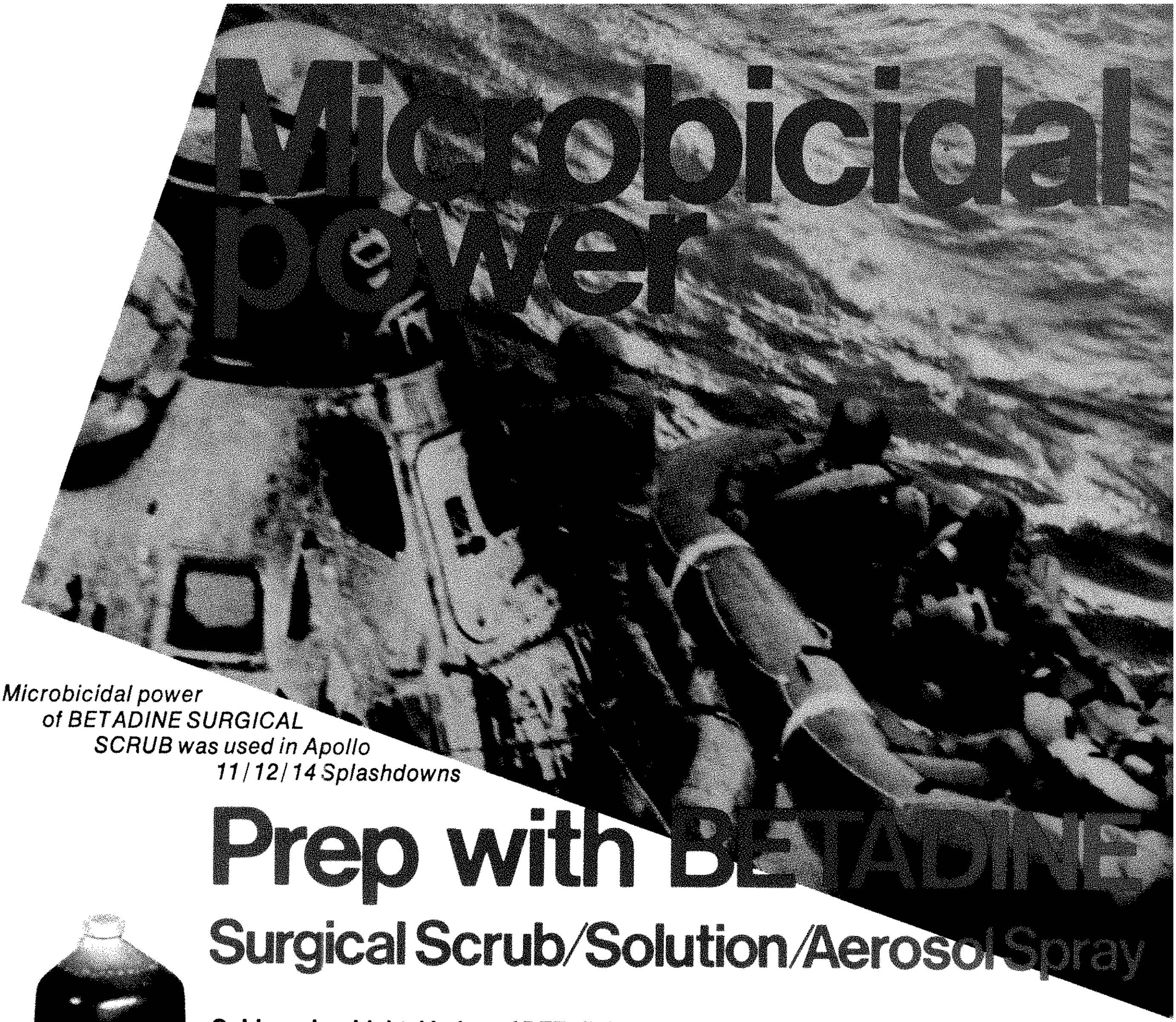

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Surgical Scrub/Solution/Aerosol Spray

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BETADINE Solution Swabsticks
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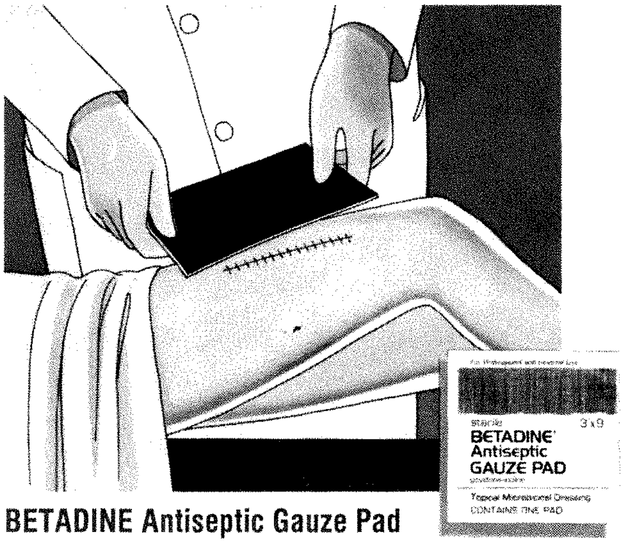

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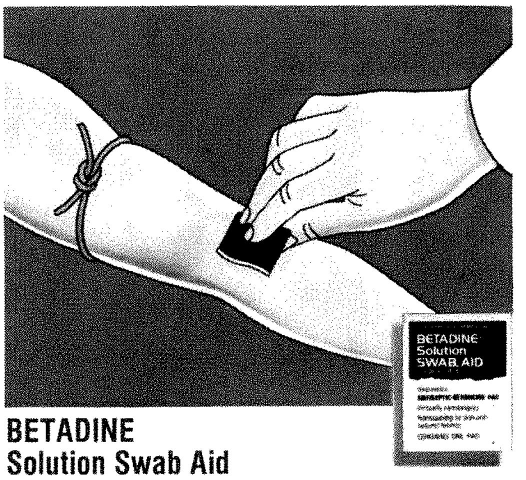

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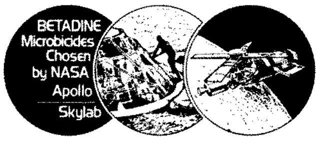

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pHisoHex contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.

to give you confidence in its use and to prevent misuse

Use as a surgical scrub.

Use as a bacteriostatic skin cleanser against staphylococci and other gram-positive bacteria.

Use at home as a hand cleanser for those who tend the bedridden patient or handle infants.

Use for washing to control outbreaks of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. Use only as long as necessary for infection control.

Do not use on burned or denuded skin or as an occlusive dressing, wet pack, or lotion.

Do not use as routine, prophylactic body wash.

Do not use as a vaginal pack or tampon, or on any mucous membranes.

Rinse thoroughly after use.

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Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control.

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components.

It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: Rinse thoroughly after use, especially from sensitive areas such as the scrotum and perineum.

If left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms. Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions.

pHisoHex should be discontinued promptly if signs or symptoms of cerebral irritability occur. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin or exposure to a powder accidentally containing approximately 6.5% hexachlorophene. Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only*. If swallowed, pHisoHex is harmful especially to

poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precautions: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, and in plastic bottles of 1 gallon.

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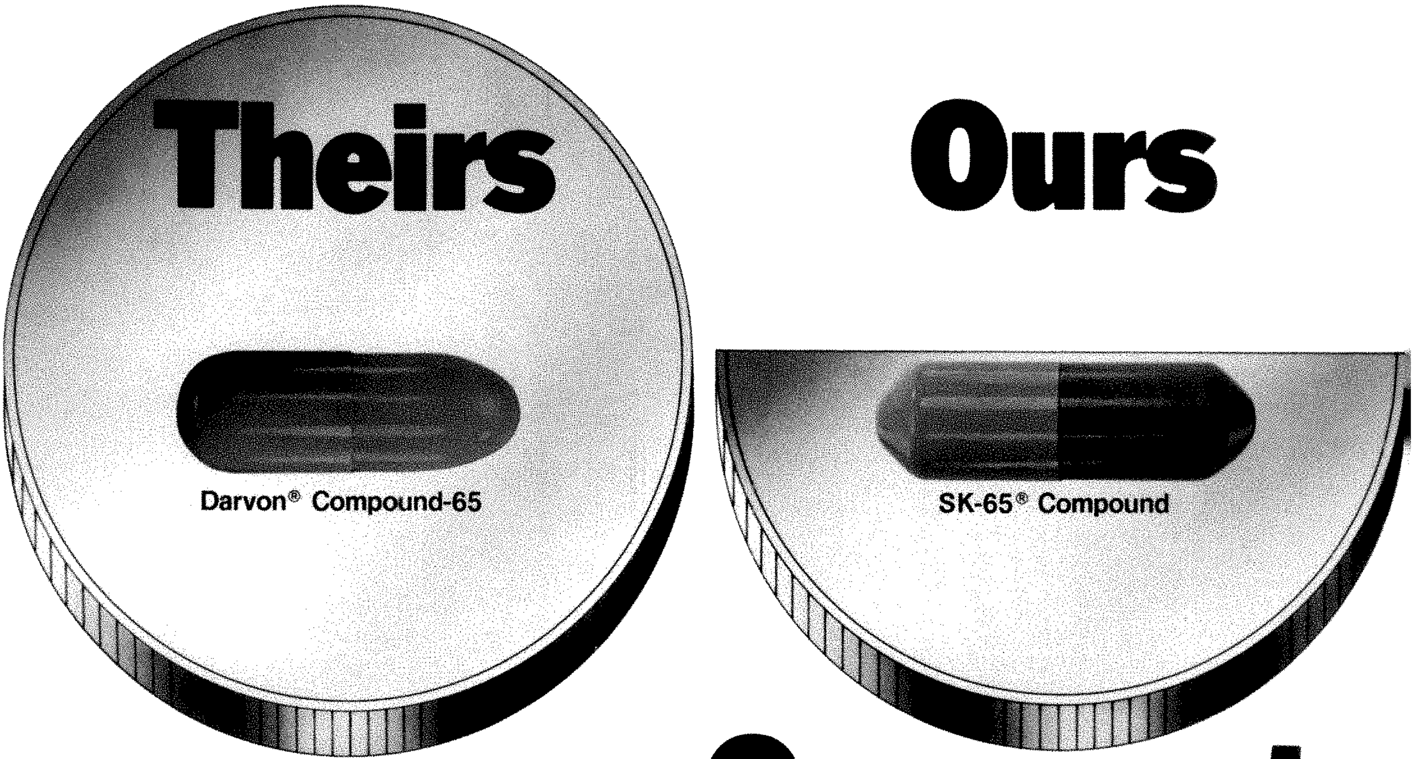

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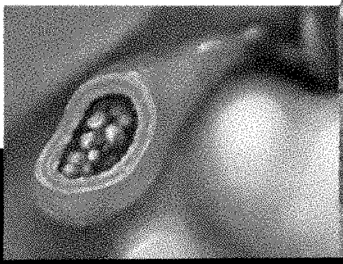
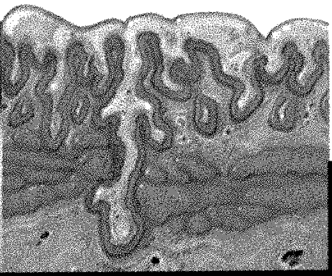
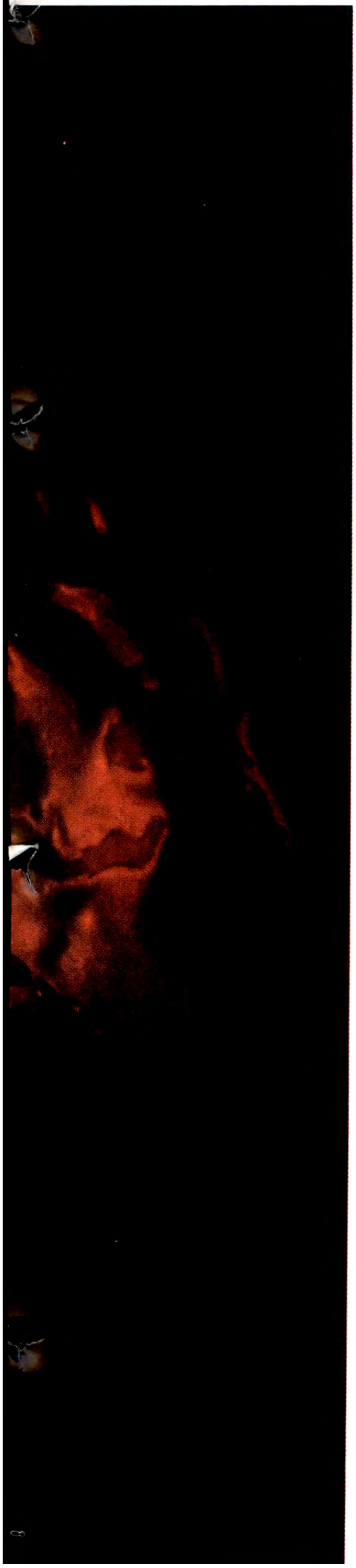




1. Artist's conception of cutaway view of gallbladder containing stones which, by causing irritation of the organ's interior wall and restricting biliary flow, may play a role in the repeated episodes of inflammation and infection associated with chronic cholecystitis.

2. Artist's conception of microscopic section of gallbladder wall showing chronic state with superimposition of inflammation, edema and necrosis due to an acute episode.

A unique view of the gallbladder, from the inside looking out.



Cholecystitis from the pathogen's point of view

Vibramycin (doxycycline) penetrates gallbladder tissue to reach susceptible[1] pathogens

Vibramycin can be useful in cholecystitis because it provides a wide antibacterial spectrum and therapeutic tissue concentrations.[2] Vibramycin is active against susceptible[1] strains of bacteria including Escherichia coli and Enterobacter aerogenes (formerly Aerobacter aerogenes).

Concentrations of oral Vibramycin in gallbladder tissue removed from four surgical patients on a dosage of 200 mg. P.O. stat and 100 mg. P.O. once daily until surgery.[2]

Patient No.	Concentration in Tissue (mcg./Gm.)
1	5.80[3]
2	1.58
3	8.68
4	7.73

[1] Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

[2] Fabre, J. et al.: Schweiz. Med. Wochenschr. 97:915, May 17, 1967.

[3] Concentration in the bile taken simultaneously: 24.2 mcg./ml.

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.
200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

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See Brief Summary on following page for information on side effects and contraindications.

Penetrates tissue to reach susceptible* pathogens...

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg doxycycline with 480 mg ascorbic acid
200-mg. vials containing doxycycline hyclate equivalent to 200 mg doxycycline with 960 mg ascorbic acid

Important facts about Vibramycin (doxycycline)

- can maintain therapeutic blood levels with a single daily infusion
- can be used without complexities of dosage alteration in patients with impaired renal function
- does not significantly elevate BUN in patients with renal insufficiency
- virtually the same broad range of indications when switching from I.V. to oral form

*Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

Vibramycin® Hyclate (doxycycline hyclate) and
Vibramycin® I.V. (doxycycline hyclate for injection)
BRIEF SUMMARY

Contraindicated: In persons hypersensitive to any of the tetracyclines.

Warnings: Use of tetracyclines during the last half of pregnancy, infancy and childhood to the age of 8 years may cause permanent discoloration of developing teeth. This is more common during long-term use of the tetracyclines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Thus, tetracyclines should not be used in this age group unless other drugs are not likely to be effective or are contraindicated. Individuals receiving tetracycline antibiotics should be advised that direct sunlight or ultraviolet light can cause photosensitivity reactions. If these reactions (exaggerated sunburn) occur, discontinue therapy. Doxycycline forms a stable calcium complex in any bone-forming tissue. Fibula growth has been decreased in prematures given oral tetracyclines 25 mg./kg. q. 6 h., but this reaction was reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

Intravenous Dosage and Administration: Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

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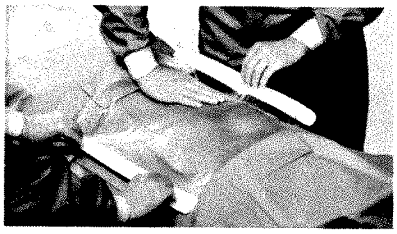
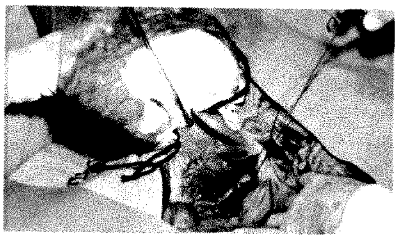


VI-DRAPE Instant Surgical Film, Sterile, applied to abdomen ready for incision

VI-DRAPE Wound Protector in place inside incision



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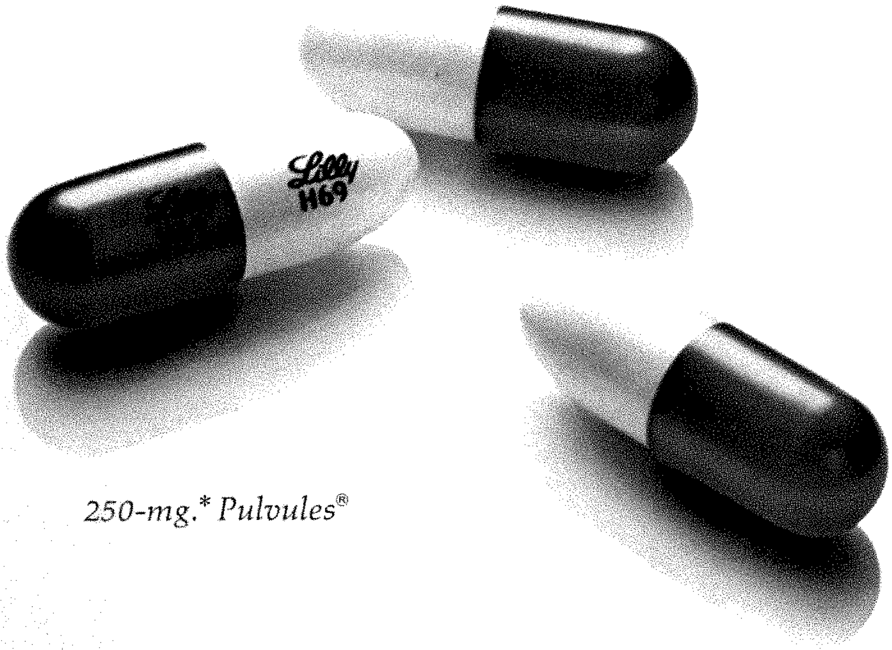

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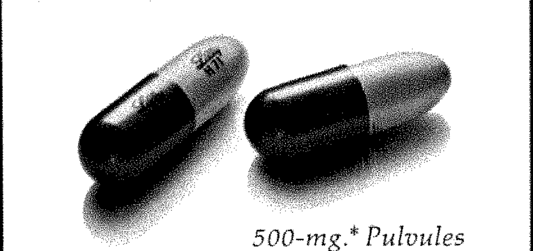

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ANNALS OF SURGERY

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Replantation of Severed Fingers

ROBERT J. CORRY, M.D., PAUL S. RUSSELL, M.D.

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Although many of the technical principles of modern vascular surgery were first brought to wide attention at the turn of the century by Carrel[3] and perfected further by many other surgeons since, application of these techniques to the anastomosis of vessels less than a millimeter in diameter has been a relatively recent advance. The development of delicate surgical instruments and the operating microscope have set the stage for major achievements in the field of microvascular surgery.

Immediate replantation of severed digits with primary vascular union of their digital arteries and veins is a potentially useful clinical area in which these techniques can be applied. Although digital artery anastomosis had been reported by Kleinert[9] in partially severed fingers in 1965, the Chinese were the first to perform a successful replantation of a completely severed digit using primary vascular union.[8] According to Professor George Wald,[14] who recently visited Peking, Chinese surgeons have replanted severed digits a number of times. A photograph of such a patient in China appears in Joshua Horn's[7] book, "Away with all Pests." The second reported case of replantation of a completely severed digit was Komatsu's[10] in Japan. He was able to rejoin a severed thumb at the metacarpal phalangeal joint using primary vascular union of the severed digital vessels. Lendvay[11] in Australia reported the successful replantation of a finger in a man who six months later lost the replanted digit as a result of trauma. Since then, according to informal reports, the Australian group has carried out a few more successful replantations of completely severed fingers. Cobbett[4] and Buncke[1,2] have ingeniously autotransplanted a great toe to the first metacarpal of a thumb with excellent results. Kleinert[13] has attempted approximately 15 replantations of totally severed fingers and four have reportedly been successful. Replantation by careful approximation of the skin without primary vascular anastomosis has been reported by Freilinger.[6]

The following case offered us an opportunity to apply the principles of microvascular surgery to the replantation of digits, and this report will describe something of what we have learned in the process.

Case Report

A 49-year-old woman completely severed the first three fingers of her right hand at her job using a paper cutting machine (Fig. 1). The middle finger was severed in the mid portion of the proximal phalanx, the index finger at the proximal interphalangeal joint, and the ring finger through the middle phalanx. She was brought immediately to the emergency room where the severed fingers were placed in iced saline to lower the tissue oxygen requirement. No attempt was made to cannulate the digital arteries for perfusion of the amputated fingers. Soon after arrival, she was moved to the operating room where, under general anesthesia, the three fingers were replanted by carrying out, in order, Kirshner wire fixation of the bone, anastomosis of each digital artery and nerve, extensor tendon suture, debridement of flexor tendons and loose closure of the skin (Fig. 2). All six digital artery anastomoses and nerve repairs were carried out under the operating microscope at 16× magnification. The arteries were primarily sutured with 9–0 Ethilon (Ethicon) tipped with a BV-3 needle. Twelve hours after replantation, arterial perfusion of all three fingers was intact and the patient was

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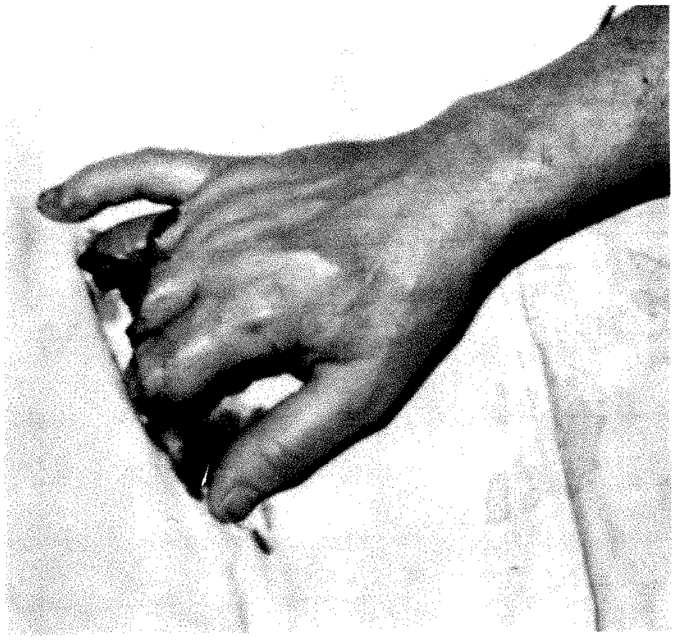

FIG. 1. Photograph of hand prior to replantation, showing levels of transection of digits. The index finger was amputated at the proximal interphalangeal joint, the middle finger through the base of the proximal phalanx and the ring finger through the middle phalanx.

returned to the operating room in an attempt to provide venous return. The venous anastomoses had not been done at the initial procedure because veins of adequate size could not be located. At the second procedure, only one severed vein was located on the dorsal surface of the index finger, and even though this vein was not carrying much of the venous effiuent blood, its ends were joined. Unfortunately, in the index finger, most of the venous return seemed to be coming from small capillaries. On the dorsal aspect of the middle finger, however, two severed veins were located and anastomosed to their respective proximal ends. By this time, arterial perfusion to the ring finger was noted to be severely impaired and several attempts to correct the spasm and clotting of the small digital artery anastomoses were unsuccessful. Therefore, the ring finger was removed at the amputation site.

During the first two weeks, the patient received Heparin, low molecular weight dextran, and Keflin. Stellate ganglion blocks were performed at three and seven days. At four days following replantation, it was clear that venous drainage of the index finger was markedly impaired, and by ten days this finger had become gangrenous and was accordingly amputated a few days later. The middle finger remained well perfused with arterial blood, and its venous drainage, although slightly impaired, was well established. By three weeks, the skin suture line had healed and only a partial thickness skin loss resulted. Skin graft coverage was not necessary and the patient was discharged at the end of the fifth week (Fig. 3). Two months later, she was readmitted for open correction of a poorly aligned fracture. Prior to operation, the brachial artery was injected with radiopaque contrast material to obtain a digital arteriogram (Fig. 4). Since only a single digital artery was patent, an incision was made on the dorsolateral surface of the proximal phalanx on the side opposite to the patent artery to avoid damage to it. The bone was shortened, reapproximated, and stabilized with two Kirshner wires. Bone chips were packed around the fracture site. Healing of the fracture was slow but complete by five months (Fig. 5).

Currently, seven months after injury, she has normal sensation of the finger tip, and is able to pick up objects and perform a variety of other tasks (Fig. 6). Since there is 45 degrees of motion at the metacarpal phalangeal joint with stable distal joints, she is able to approximate easily the tips of the thumb and rejoined middle finger. She is quite pleased with the present result both cosmetically and functionally.

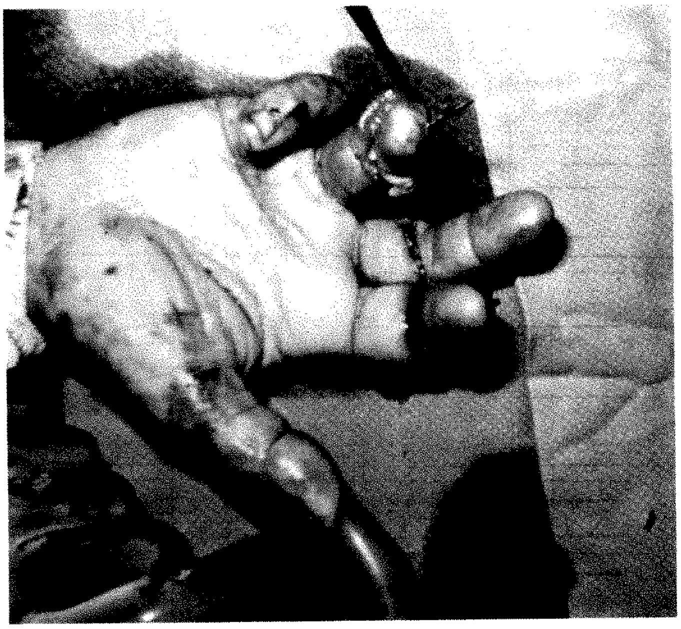

FIG. 2. The injured hand immediately after replantation of all three severed fingers. The fingers are well perfused with arterial blood. Venous anastomoses had not yet been carried out.

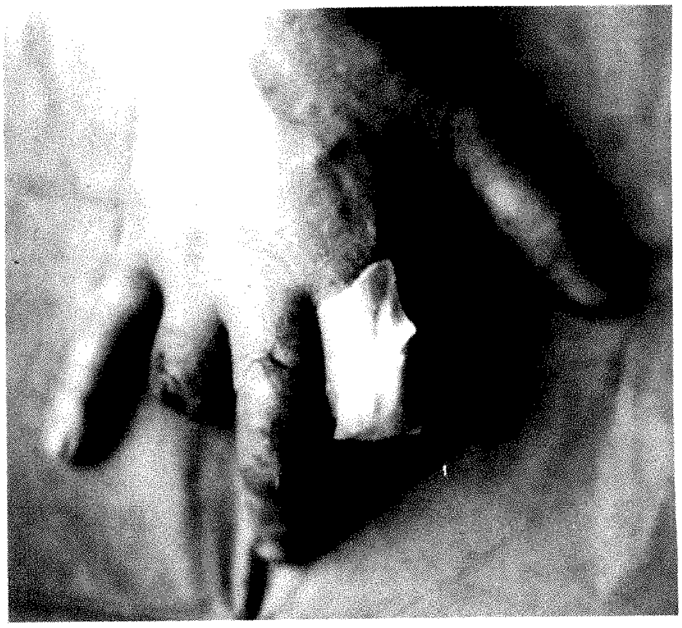

FIG. 3. Four weeks after injury. The middle finger has healed. The index and ring fingers have been reamputated (see text).

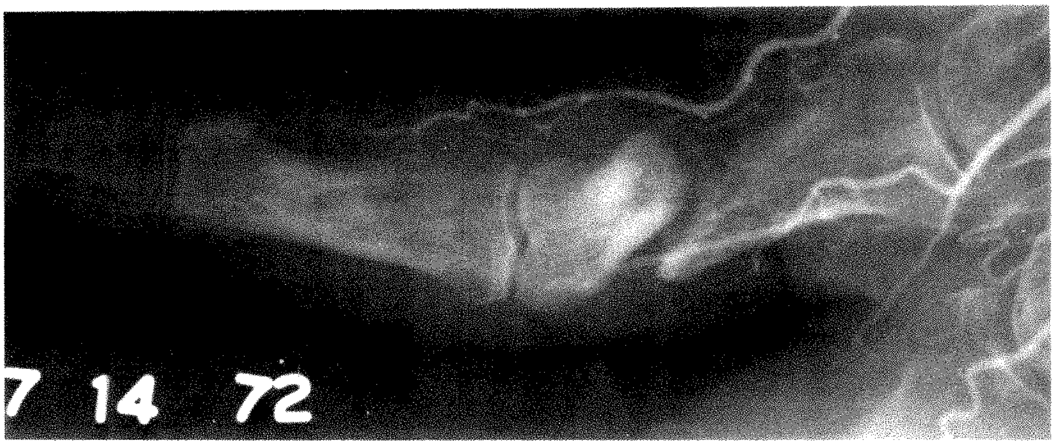

Fig. 4. Arteriogram showing a single patent digital artery and poor alignment of the phalangeal fracture. The fracture was realigned and stabilized at this time.

Discussion

This case illustrates some important principles of digital replantation. Prior to attempting replantation of an amputated finger, the degree of tissue damage at the amputation site should be carefully assessed. It may be necessary to debride devitalized and necrotic tissue, and in the process, some shortening of the finger may be necessary. Obviously, if the soft tissues, in particular the arteries and veins, are severely damaged as may occur in a crushing or twisting injury, replantation would probably not be advisable. However, if the amputated finger is not severely damaged, then one is justified in proceeding with an effort at replantation. Proper alignment and stabilization of the bones must be accomplished prior to carrying out the vascular anastomoses as Malt[12] and his coworkers have emphasized with severed arms. Priority is given in the same way to the Kirshner wire stabilization of amputated fingers. The subsequent healing of the fracture site depends upon precision of alignment. In our case, if the severed proximal phalanx of the middle finger had been more precisely stabilized, a second operation might have been avoided. If necessary, the bone may be shortened slightly to prevent tension on the vascular anastomoses and the skin closure.

Careful attention to the details of technique is essential for success. The ends of the severed digital arteries should be freshened. Damage to the intima must be avoided at all costs, if dilatation of the vessel ends is necessary. A loop of 6–0 silk placed around the artery about a centimeter proximal to the severed end is tied with a single knot to provide temporary occlusion while the anastomosis is being carried out. Precise eversion of the vessel walls must be accomplished at the site of anastomosis to provide a smooth intimal surface and thus prevent subsequent platelet aggregation and intravascular coagulation. If even a small flap of adventitia protrudes into the lumen of such a tiny vessel, a nidus for platelet aggregation is provided. There is some discussion in the literature as to use of an interrupted or continuous suture line in constructing an anastomosis between severed vessels ends as small as a digital artery. In the laboratory, we have found that a carefully placed continuous suture without tension provides better eversion of the intima than multiple interrupted sutures.[5] In using the continuous suture technique, however, one must avoid constriction of the anastomosis. Prevention of a pursestring effect can be accomplished best by suturing the anastomosis between three equidistantly placed interrupted sutures.

After completion of each arterial anastomosis, it is worth taking a few additional minutes to approximate the ends of the severed digital nerve. At the digital level, in contrast to more proximal amputations of the upper

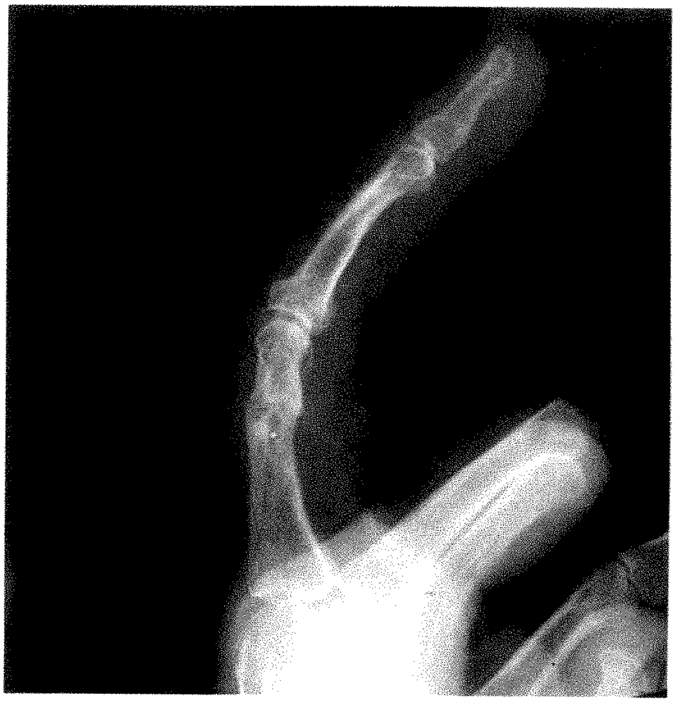

Fig. 5. Five months after injury showing proper alignment of the fracture site and healing with callous formation. Bone chips had been used at the time of resetting the fracture.

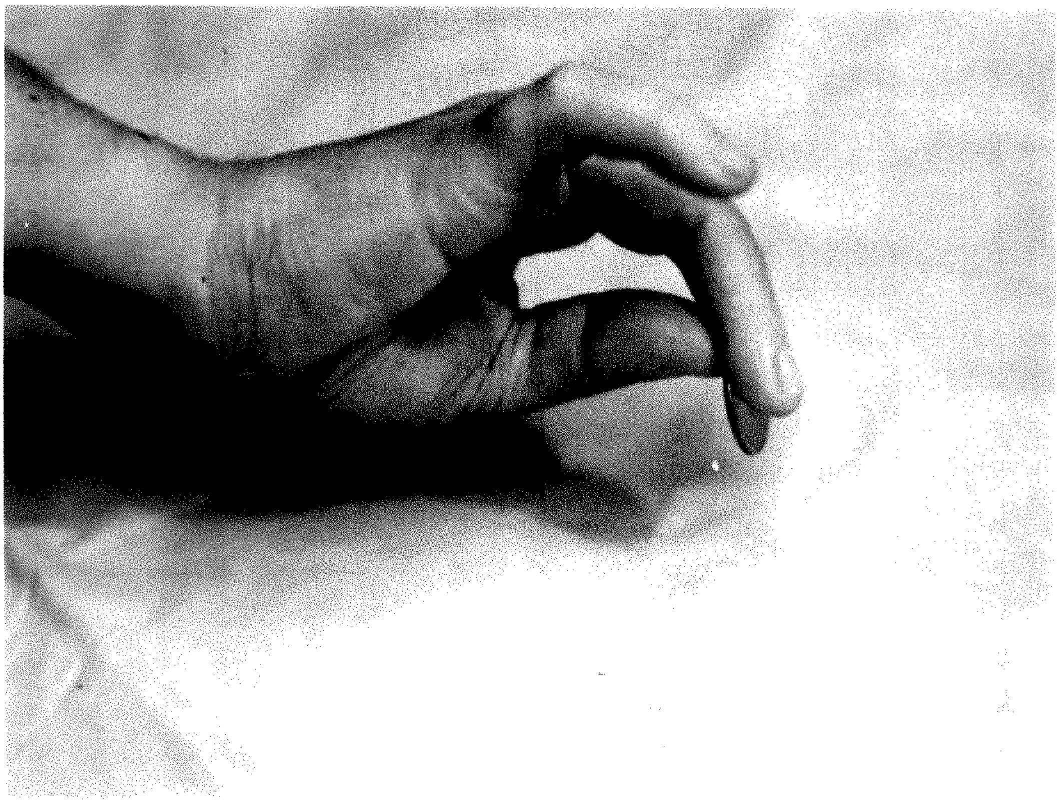

FIG. 6. Seven months after injury. The patient is now able to pick up small objects using finger-thumb approximation and has normal sensation of the middle finger.

extremity, the nerves are entirely sensory and repair should not be postponed until a second operation as is recommended with severed arms.* Early return of sensation to the tip of the replanted finger enhances finger to thumb approximation and thus early use of the finger. Furthermore, if nerve repair is postponed, dissection of the severed ends in the scar tissue around the neurovascular bundle would risk inadvertant damage to a previously repaired digital artery.

One of the most important requirements of successful replantation is to provide venous return of blood from the replanted finger by anastomosing the veins located just beneath the skin on the dorsal surface of the finger. Reattachment of incompletely severed fingers by arterial anastomosis alone has had a high success rate, undoubtedly due in large measure to the presence of undamaged venous channels in the small piece of skin by which the finger is attached. This advantage does not accompany the completely severed finger, where careful approximation of at least one severed vein must be carried out at some stage to provide a channel for venous drainage. It is possible, of course, that veins could unite by themselves, but it is far better to join them intentionally to ensure adequate venous return. The importance of establishing venous drainage is illustrated in our case. A large enough vein carrying blood from the index finger, rejoined at the proximal interphalangeal joint, could not be found. When the skin suture line sealed so that venous blood no longer drained into the dressings, the index finger became cyanotic and congested, and within a few days, frankly necrotic. Since veins of adequate size in the middle finger carrying venous effluent blood were joined to similarly sized transected veins on the proximal side of the severed finger, venous return of this finger, although slightly impaired for the first ten days, was never in doubt.

Meticulous attention to the prevention of sepsis along the skin suture line is of great importance. During the first two weeks, our patient was placed in isolation and dressings were changed twice daily using gown, mask and glove isolation procedures. The hand should be covered at all times with a bulky sterile dressing until the skin suture line is healed. Systemic prophylactic antibiotics should be used initially, and results of frequent cultures of the suture line should determine the subsequent choice of antibiotics.

Other potentially important auxiliary measures used in the postoperative period include systemic anticoagulation and the administration of low molecular weight dextran. The intravenous injection of Heparin for ten days to two weeks serves to reduce the chance of intravascular coagulation both at the anastomoses and in small vessels and capillaries within the replanted digit. The advisability of adding low molecular weight dextran to the therapeutic regimen is uncertain. For example, if venous congestion is marked, increased flow into the replanted finger resulting from the administration of low molecular weight dextran might, in theory, increase venous congestion. If arterial inflow is impaired as a result of vasospasm, a stellate ganglion block may be helpful.

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* Personal communication.

Edema of the finger proximal to the level of transection is perhaps one of the most critical problems encountered within the first two weeks. If swelling becomes severe, impairment of venous drainage and eventual obstruction of arterial inflow can result. Elevation and immobilization serve to prevent edema and consequent vascular impairment.

A finger severed at or beyond the proximal interphalangeal joint would be difficult to replant successfully, as in our case, since the diameter of digital arteries and veins at this level is much smaller than at the proximal phalangeal level. Fortunately, a distally amputated finger results in considerably less disability for most patients.

While loss of two or more fingers is a major disability, the loss of a thumb is an even greater one. If immediate replantation is not possible, an elective great toe to thumb autotransplant, after the method of Cobbett and Buncke, should be considered.

Industrial medical personnel should be aware of emergency procedures to be followed immediately after injuries of this kind. The transected finger is placed in sterile iced saline, and the amputation site cleansed and dressed with sterile gauze. The patient should be transported to the nearest hospital where microvascular surgery is performed. No attempt to cannulate the digital arteries for perfusion of the transected finger need be made because of the risk of damaging the delicate intima of these small vessels. If correct emergency procedures are followed, successful replantation up to at least 12 hours after the injury should be possible.

Summary

The replantation of fingers severed distal to metacarpal phalangeal joints utilizes well established principles of vascular surgery on a miniature scale. Success depends in large part upon the technical precision of the arterial and venous anastomoses. The indications for replantation of an amputated finger include loss of a thumb, loss of two or more fingers, or loss of a single finger at the proximal phalanx. Loss of a single finger beyond the proximal interphalangeal joint would not represent a major disability for most patients and the absence of adequate veins at this level make success unlikely. The case described serves to illustrate several of the important features of replantation of totally amputed fingers, and suggests that procedures of this sort will be performed more often in the future.

Addendum

The patient is now 19 months after replantation with a satisfactory result. The Shanghai group, has had success in over 50% of about 100 finger replantations (Malt, R. A. and McDowell, F.: Cabal from Cathay. (editorial) N. Engl. J. Med., 288:1353, 1973).

Acknowledgments

The authors wish to express gratitude to Drs. John Constable and Edward Nalebuff for their valuable advice in the postoperative management of the case presented.

References

1. Buncke, H. J., et al.: Exhibit at the Fourth International Congress of the Transplantation Society. San Francisco, Sept. 1972.
2. Buncke, H. J. and Schulz, W. P.: Experimental Digital Amputation and Reimplantation. Plast. Reconstr. Surg., 36:62, 1965.
3. Carrel, A.: La Technique Operatiore des Anastomoses Vasculaires et la Transplantation des Visceres. Med. Lyon., 98:859, 1902.
4. Cobbett, J. R.: Report of a Case of Transfer of a Great Toe to Replace an Amputated Thumb. J. Bone Joint Surg., 51B:677, 1969.
5. Corry, R. J. and Russell, P. S.: New Possibilities for Organ Allografting in the Mouse. *In* Immunological Aspects of Transplantation Surgery. Calne, R. Y., editor. Oxford and Lancaster, Medical and Technical Publishing Co., Ltd., (In press.)
6. Freilinger, G.: Reimplantation in Traumatic Amputations. Klin. Med., 21:386, 1966.
7. Horn, Joshua A.: Away with all Pests. London, Monthly Review Press, 1969.
8. Hwa, W.: Chinese Surgeons Break Another World Medical Barrier. Acto Med. Philip., 3:221, 1967.
9. Kleinert, H. E. and Kasden, M. L.: Anastomoses of Digital Vessels. J. Kentucky Med. Ass., 63:106, 1965.
10. Komatsu, S. and Tamai, S.: Successful Replantation of a Completely Cut Off Thumb. Plast. Reconstr. Surg., 42:374, 1968.
11. Lendvay, P. and Owen, E.: Microvascular Repair of Completely Severed Digit. Fate of Digital Vessels after Six Months. Med. J. Aust., 2:818, 1970.
12. Malt, R. A. and McKhann, C. F.: Replantation of Severed Arms. JAMA, 189:114, 1970.
13. Medical World News: Tools that Extend the Surgeon's Skill. Jan. 1973, p. 67.
14. Wald, G.: Guests of the Management. Harvard Bulletin, April, 1972, p. 43.

The Extended Extrapleural Radical Mastectomy:

Its Role in the Treatment of Carcinoma of the Breast

SAUL F. LIVINGSTON, M.D., MYRON ARLEN, M.D.

DURING THE PAST DECADE, several surgical methods have come into vogue in terms of treating the patient with primary carcinoma of the breast. These range from lumpectomy[4] to the extended radical mastectomy,[25,29] with each method having a proponent advocating reasons for suitability based on immunologic or anatomic criteria.[10,24] The opinion still voiced among surgeons is that mastectomy with regional node dissection is the method offering the best opportunity for cure.[1] The present study was undertaken to evaluate the role of the extended mastectomy in terms of internal mammary chain involvement and the effect of removing these nodes on the overall survival rate. All patients in the present study with primary operable carcinoma of the breast were subjected to radical mastectomy and removal of the internal mammary node chain. The usual contraindications to radical mastectomy were employed and include: (1) primary tumor fixed to chest wall, (2) fixed axillary nodes, (3) ulceration of skin due to carcinoma or satellite nodules in the skin of the breast (4) palpable supraclavicular lymph nodes (5) inflammatory carcinoma of the breast, (6) edema of the arm, and (7) distant metastasis. Each patient was examined preoperatively, recording the site of the primary tumor. X-rays of the chest, skeletal survey and electrocardiogram were performed prior to the operation. An extended radical mastectomy, including extrapleural resection of the internal mammary nodes, was performed on all patients in this series; those over 65 years of age and all with medical contraindications underwent either the standard or modified radical mastectomy.

From the Department of Surgery, The Jewish Hospital & Medical Center of Brooklyn and The State University of New York, Downstate Medical Center

Methods and Material

All of the operative procedures in the present study were performed by the senior author. Five hundred-and-eighty-three patients underwent extended radical mastectomy between 1955 and 1970. These patients were evaluated for incidence of nodal involvement as related to the quadrant of the breast in which the tumor arose. Three hundred-and-seventy-three of the patients were suitable for evaluation of 5-year survival rates. The ages of these patients fell primarily into the 40–49 and 50–59 year groups, between which there were 139 and 136 respectively (Table 1).

The operation consisted of the classical Halstead radical mastectomy followed by extrapleural resection of the internal mammary chain. Skin flaps were developed and muscles were divided to expose the contents of the axilla. Level III lymph nodes were removed first and marked for identification. Other levels were similarly labelled. The pectoralis major was separated from its sternal attachments to expose the second, third and fourth costal cartilages. An incision was made in the third interspace through the intercostal muscles to its endothoracic fascia. With careful dissection, the third costal cartilage was separated from the endothoracic fascia and pleura. Intercostal vessels were tied at the costochondral junction. The cartilage was then cut at the costochondral junction and subluxated from the sternum. The procedure was repeated for the fourth and finally

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second costal cartilages. The parasternal area was opened to expose the internal mammary vessels and lymph nodes. Ligatures were placed around the vessels on the undersurface of the first rib and upper end of the 5th rib. The internal mammary chain was then gently brushed off the pleura and removed en bloc with costal cartilages and intercostal muscles. The space between the sternum and cut ends of the rib cage were left open, no prosthetic device being employed. Operative time was approximately 4 to 5 hours.

TABLE 1. *Age Distribution of Patients Treated by Extended Extrapleural Radical Mastectomy*

Age	Number of Patients
24	1
29	1
30–39	50
40–49	139
50–59	136
60–68	46
Total	373

Results

The extended extrapleural radical mastectomy was found to be an uncomplicated procedure, with no mortality and few postoperative complications. Mobidity resulted from occasional skin necrosis and from inadvertent entry into the pleural cavity.

Two hundred-and-ninety-six of the resected tumors in the overall series of 583 patients were found to be located in the outer quadrant of the breast. Ninety-seven lesions were found in the inner quadrant, 153 were centrally located and 37 arose in the nipple area. Each of the lesions was catagorized in terms of its association with histologically positive or negative internal mammary nodes (Table 2).

Analysis of the 296 patients with outer quadrant lesions revealed that 165 had negative and 131 had positive axillary nodes. When the axilla was negative, there was a low incidence of positive internal mammary nodes (5%). When axillary nodes were involved with tumor, the overall incidence of involvement increased to 23%. Among the 97 patients with inner quadrant lesions, 70 had neither clinical nor microscopic evidence of axillary disease; 27 did have positive axillary nodes. A similar relationship between positive axillary nodes and internal mammary spread was noted again. Negative axillary nodes were associated with a 14% incidence of internal mammary node involvement. When the axilla was positive, this group demonstrated a 59% incidence of metastasis to the internal mammary chain. Centrally placed tumors metastasized to the axilla in approximately one-third of cases. In this group of patients, 43% of the internal mammary nodes removed were found to contain metastatic tumor. The highest incidence of internal mammary node involvement occurred in the 11 nipple lesions with positive axillary nodes. Seven of these patients (63%) had concomitant internal mammary node tumor metastasis.

The overall incidence of internal mammary node involvement by tumor appears directly related to concomitant tumor spread to axilla, as well as the position of the tumor in the breast. When axillary nodes were negative, 8% of the overall group of patients had internal mammary node involvement. When the axillary nodes were positive, the overall incidence of substernal node metastasis was 32%.

One of the reasons for failure to control local disease was the appearance of chest wall metastasis. Among the 373 patients analyzed in terms of survival, 24 developed chest wall recurrence without evidence of distant metastasis. Five additional patients developed chest wall disease concomitant with systemic dissemination of tumor. These 29 cases represent a 7.7% incidence of local recurrence of tumor. There were no patients with recurrent axillary or parasternal disease. When local disease recurred within the first two years of surgery, the overall prognosis was poor. Twenty-two of the patients in this series developed disease during this interval and expired before 5 years. Four patients developed recurrence 3 years postmastectomy and survived 5, 7, 8 and 9 years. Three patients developed recurrence 3, 7 and 8 years postoperatively and survived with disease 12, 14 and 15 years respectively.

Local chest wall recurrence was next evaluated in terms of nodal disease found at surgery. Among the 204 patients where all node-bearing areas were found to be free of disease, 6 patients (3%) developed recurrence in their chest wall. When axillary nodes were negative, but internal mammary nodes found to be positive, 2 patients

TABLE 2. *Extended Extrapleural Radical Mastectomy Analysis (583 cases, 1955–1970)*

No.	Outer			No.	Central		
165	AX−	IM−	157(5%)	97	AX−	IM−	87(10%)
	AX−	IM+	8		AX−	IM+	10
131	AX+	IM−	101(23%)	56	AX+	IM−	32(43%)
	AX+−	IM+	30		AX+	IM+	24
296	Overall		13%	153	Overall		22%
	Inner				Nipple		
70	AX−	IM−	60(14%)	26	AX−	IM−	26
	AX−	IM+	10		AX−	IM+	0
27	AX+	IM−	11(59%)	11	AX+	IM−	4(63%)
	AX+	IM+	16		AX+	IM+	7
97				37			
	Overall		27%		Overall		20%
18% Positive Internal Mammary							
AX−	8% IM+						
AX+	32% IM+						

of 15 or 13% showed local recurrence of tumor. In the 104 patients with positive axillary and negative internal mammary nodes, 8 patients (8%) developed recurrent local disease. When both of the major lymph node areas were involved by tumor, an anticipated increase in local recurrent tumor was seen. Among the 50 cases in this group, 8 or 16% manifested signs of recurrent tumor (Table 3).

Three hundred-and-seventy-three of the patients in the present study were evaluated in terms of 5-year survival with and without disease (Table 4). When both internal mammary and axillary nodes were negative, 175 of the 204 patients in this group were free of disease. An additional 6 patients were alive but with disease present. The overall 5-year survival rate free of disease in the group where no lymph node metastasis were noted, was 85%. When the internal mammary nodes were involved by tumor and the axilla remained free, the 5-year survival clinically free of disease was 53%. When nodal metastases were limited to the axilla, a similar 5-year rate free of disease was noted.

In terms of overall 10-year survivals, 102 of 172 patients studied (60%) were clinically free of disease (Table 5). In this group the absence of any metastatic nodes at the time of surgery resulted in an attrition rate of 7% over the 10-year period; the survival rate free of disease dropped from 85% to 78% during this time (Table 6). It is of interest that when nodes in the axilla were found to be positive with associated negative internal mammary chain, the 5 and 10-year survival rates differed little. When axillary and internal mammary nodes were found to be positive at surgery, the 10-year survival rate free of disease decreased from 32% to 17%. The overall survival rate free of disease for the entire group of patients in this study dropped from 68% 5-years to 60% at the 10-year level.

Discussion

In the patient with carcinoma of the breast, undergoing the classical radical mastectomy, only a portion of the regionally draining nodes is removed. Anatomically, while 75% of the lymphatic channels drain to the axilla, a significant flow (25%) is directed to the internal mammary chain.[22] This suggests that the latter group of nodes represents an important pathway for the spread of carcinoma in the breast.[24]

TABLE 3. *Extended Extrapleural Radical Mastectomy: Local Recurrence in Group of 373 Cases*

Para-sternal Recurrence	Chest Wall Recurrence	Chest Wall and Disseminated Disease	Axillary Recurrence
204 AX − IM −	6(3%)	0	0
15 AX − IM +	2(13%)	0	0
104 AX + IM −	8(8%)	1	0
50 AX + IM +	8(16%)	4(8%)	0
Totals 0	24	5	0

TABLE 4. *Extended Extrapleural Radical Mastectomy Two Series 1955–1960; 1960–1965 Result in 373 Patient—5 Year Follow-up*

No.	N E D	%	Survival	%
204 AX − IM −	175	85%	181	89%
15 AX − IM +	8	53%	9	60%
104 AX + IM −	54	52%	63	61%
50 AX + IM +	16	32%	25	50%
34 APEX −	16	47%	22	65%
16 APEX +	0	0	3	19%
Overall				
373 Cases N E D	253	68%		
373 Cases Survival	278	75%		

Proponents of a lesser than mastectomy procedure[3] have suggested that an immune defense mechanism or barrier develops within the intact node system and that these nodes resist local spread of tumor.[4] It is therefore implied that clinically negative nodes be left undisturbed. No study exists, however, which can implicate the regionally draining nodes as the sole factor in host tumor immunity, should it exist. It is more probable that if an immune response does develop, it is a systemic one and will not be altered by partially interrupting any one pathway. What is important, therefore, is the consequence of leaving regional nodes behind, nodes which may be involved by tumor and which may act as foci for recurrent and metastatic disease.

Clinical attempts at evaluating nodal involvement have been notoriously inaccurate. Coleman and Barry[2] noted that among 898 patients with clinically negative nodes, 41.1% had microscopic tumor involvement. Stender[23] reported that in Stage I carcinoma of the breast, metastases usually involve 30% of the cases considered to have clinically negative axillas. These factors must be taken into consideration when one decides that nodes are to be spared for the sake of their immunologic capabilities. If an immunologic defense mechanism were in existence, as one might predict in the presence of medullary carcinoma of the breast with concomitant sinus histiocytosis,[21] then metastasis to regional nodes would be uncommon and one might predict an improvement in survival. In actuality, when lesions classified as medullary carcinoma reach 2.5 cm. or more in diameter the incidence of nodal metastasis becomes greater than 20%, and in such instances there is a concomitant dimunition in survival rate.[9]

In the present study, an attempt was made to evaluate the significance of internal mammary node involvement by tumor and to determine possible improvement in survival resulting from resection of these nodes. Previous studies have suggested that tumor spread to the internal mammary chain may be important in the natural history of breast carcinoma;[17] that determining their incidence of involvement can be valuable in prognosticating the course of events, and that their removal may have a salutory effect on end-results of the disease. Several studies have been performed that have been helpful in selecting those patients in the high risk category.[27] Donnigan[5] noted that in the laterally placed lesions, where the axilla was considered clinically free of disease, a 4% incidence of internal mammary spread occurred. This increased to 13% with medially placed tumors. Veronesi[28] found that in instances of clinically palpable axillary disease the internal mammary nodes were involved in as many as 42% of patients undergoing surgery. Review of data in the present study indicated that lateral quadrant lesions had a low ratio of internal mammary nodes to axillary node involvement. When axillary disease became clinically evident however, a shift in balance favoring mediastinal node involvement resulted. For the overall group of patients studied, the presence of axillary nodes suggested that a high degree of internal mammary node metastasis would be found (32%). Negative axillary nodes were associated with an 8% involvement by metastatic disease to the internal mammary chain. The highest incidence of internal mammary node metastasis occurred with primary inner quadrant and nipple lesions. In these patients, positive axillary nodes were associated with 59 and 63% incidence of internal mammary node disease respectively.

Among the 373 patients followed for 5 years, 169 (45%) had at least one site of nodal disease; 65 (17%) had disease involving their internal mammary chain (Table 4). Internal mammary nodes from the 1st to 4th intercostal spaces were removed for evaluation at the time of surgery. The highest incidence of positive nodes was found in the second interspace.

Several reports have suggested that minimizing the extent of resection at the time of surgery offers fewer complications,[12,13] better cosmetic results and survival rates comparable to those seen with radical mastectomy.[18] These studies were usually performed in selected patients having small primary lesions and minimal, if any, axillary disease.[1] In spite of this, there appeared to be a higher incidence of local recurrence, a factor known to be associated with diminished long-term survival.[14] Handley and Thackrey,[12,13] employed the conservative radical mastectomy in a selected series of 143 patients over a 10-year period. The incidence of local recurrence in their hands was 22% (Table 7). Rissanen[19] described results in the treatment of 1,008 cases managed between 1948 and 1961. Four hundred-and-fifteen were offered local excision and postoperative radiation therapy. Five hundred-and-ninety-three patients were managed by radical mastectomy with pre and postoperative radiation therapy. Local recurrence developed in 107 patients (25.8%) where limited surgery had been performed. Thirty-nine of these patients required further excision plus radiation therapy and 68 went on to either simple or radical mastectomy. In the group undergoing radical mastectomy, the local recurrence rate was 9.5%. Employment of the classical radical mastectomy at Memorial Hospital was associated with a similar decrease in incidence of chest wall recurrence. Among 555 patients undergoing radical mastectomy the incidence of local recurrence was noted to be 1.3% when there was no evidence of any nodal metastasis.[7] This increased to 24.8% when axillary metastasis was clinically present. Farrow[8] studied two groups of patients having similar sized lesions and theoretically the same stage of disease. One group (77 patients) was treated by radiation after aspiration or incisional or excisional biopsy plus radiation. Forty-seven of these patients (61%) developed signs of local recurrence. When radical mastectomy was employed 9.1% of the patients developed evidence of locally recurrent disease.

TABLE 5. *Extended Extrapleural Radical Mastectomy 1955–1960 10-Year Follow-up to 1970 Result in 172 Patients*

No.	N E D	%	Survival*nts*	%
90 AX− IM−	70	78%	74	82%
8 AX− IM+	3	38%	3	38%
50 AX+ IM−	25	50%	27	54%
24 AX+ IM+	4	17%	4	17%
15 APEX−	4	27%	4	27%
9 APEX+	0	0	0	0
	Overall			
172 Cases	N E D	102	60%	
172 Cases	Survival	108	63%	

In the present study, where internal mammary node dissection was employed as part of the mastectomy, 7.7% of the cases developed local recurrence. When axillary and internal mammary nodes were found to be negative, the incidence of local recurrence was 3%; when axillary and internal mammary nodes were positive, 16% of the group developed evidence of local chest wall disease. One can speculate that procedures which fail to implement removal of regionally draining lymph nodes, especially those with metastatic disease, tend to allow an

TABLE 6. *Extended Extrapleural Radical Mastectomy*

	N E D		Survival	
	5 Years	10 Years	5 Years	10 Years
AX− IM−	85%	78%	89%	82%
AX− IM+	53%	38%	60%	38%
AX+ IM−	52%	50%	61%	54%
AX+ IM+	32%	17%	50%	17%
Apex−	47%	27%	65%	27%
Apex+	0	0	19%	0
Overall	68%	60%	75%	63%

TABLE 7. *Local Recurrence within 10 Years*

Author	No.	(*Columbia Clinical Classification*) Nature of Primary Treatment	Parasternal	Chest Wall	Axilla	Survival 10 Years
R. S. Handley	143	Conservative radical (Patey + radiation)	8 5.6%	29 20%	3 Cases	43%
Kaae & Johansen ABC	196	Simple mastectomy + deep X-ray McWhirter	1 1%	20 10%	20 10%	45%
Haagensen & Cooley ABC	584	Entire series radical mastectomy + 39 cases referred for radiation Positive Apex or Internal mammary biopsy 10%	24 4%	42 7%	3 Cases	53%
Livingston	373	Extended extrapleural radical mastectomy + radiation for + axilla AX+ 43% IM+ 19% APEX + 28%	0	29 7.7%	0	60% NED 147 cases 63% survival
Farrow, Fracchia, Robbins, Castro	17	Excisional biopsy + radiation	6 patients had subsequent radical 1 simple			1 patient alive had radical mastectomy.

increase in the appearance of local tumor and as a reflection of this, decrease survival rate.[6]

Attempts to justify a high incidence of local recurrence following simple mastectomy have been made with the assumption that further surgery could always be employed with equally good results.[4] In the present study, 29 patients did develop chest wall recurrence; 22 died before 5 years irrespective of additional therapy that was offered to the site of locally recurrent tumor.

In most series evaluated, there appears to be a theoretical improvement in survival when lymph node areas clinically considered to be involved are removed as part of the operative procedure.[11,26] Lewisohn[16] reported a 48.7% overall 10-year survival rate at Johns Hopkins Hospital when patients underwent the classical radical mastectomy. Farrow noted that the 10-year overall survival rate for the radical mastectomy group in his series, was 49.4%. Leak[15] similarly noted that there was at least a 20% greater survival rate for patients undergoing radical mastectomy than in those having a lesser procedure. When the internal mammary chain was additionally removed as part of the radical mastectomy operation, a further improvement in survival was noted.[20] Urban reported that, in 315 patients undergoing internal mammary node dissection, he was able to achieve a 5-year survival rate of 65.8% free of disease and a 10-year survival rate of 54% free of disease.

In the present study, where extrapleural resection of internal mammary nodes was added to the operative procedure, the overall 10-year survival rate free of disease was found to be 60%. Among the patients in this group having negative axillary and internal mammary nodes, 78% survived free of disease for 10 years. Where the both node-bearing areas were positive, a 17% survival rate free of disease was achieved. When internal mammary nodes were involved and axilla was not only clinically, but microscopically negative, 38% of the patients remained free.

In this latter group, one would expect that the classical radical mastectomy would have overlooked the presence of metastatic disease and that further metastasis would have developed. A comparison of overall survival rates for various surgical series is seen in Table 7. There appears to be a progressive improvement in ten-year survival as more attention is given to the extirpation of the regional nodes draining the tumor. We see a 10-year survival rate of 45% for simple mastectomy plus radiation, a 53% survival for the standard radical mastectomy and 60% survival free of disease for the extended radical mastectomy.

To establish if the differences in survival for the various groups were statistically significant, the CHI square test was applied. Here, to establish significance, a P value (probability) of 0.05 must be obtained. When the survival data for the standard mastectomy was compared to the simple mastectomy plus radiation, a CHI square value of 3.64 was obtained with a P value approximating 0.05 suggesting that the improved survival in the radical mastectomy group was probably significant. When the extended mastectomy (present study) was compared to the classical radical, CHI square was found to be 6.5 with a P value of 0.01 establishing more dramatically improvement in overall survival. One must conclude from this information that adequate control of all sites of nodal involvement remains the crucial factor in managing this disease entity.

Summary

A review of several operative series describing the surgical management for patients with breast carcinoma appears to suggest that the standard radical mastectomy is a superior operation to one where lymph nodes are left behind. This is reflected in several parameters including the incidence of local recurrence and improvement in 5 and 10-year survival rates. The addition of the internal mammary node resection to the classical radical

mastectomy is recommended when one suspects a high incidence of internal mammary disease. The operation not only appears to add to the survival rate, but also provides an accurate means of assessing the presence or absence of nodal metastasis, allowing for the better evaluation of overall prognosis and for possible further treatment. In the present study, where an extrapleural internal mammary node dissection was added to the operative procedure, the overall 10-year survival rate free of disease was found to be 60%. When both node-bearing areas were found to be positive, a 17% survival rate free of disease was achieved and when the internal mammary nodes alone were involved, 38% of the patients remained free of disease for 10 years.

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References

1. Anglem, T. J. and Leber, R. E. The Dubious Case for Conservative Operation in Operable Cancer of the Breast. Ann. Surg., 176:625, 1972.
2. Coleman, G., Barry, N. and Robbins, G. F.: Inaccuracy of Clinical Examination of the Axilla. James Ewing Society, Annual Symposium, 1954.
3. Crile, G., Jr.: Rationale of Simple Mastectomy without Radiation for Clinical Stage I Cancer of the Breast. Surg. Gynecol. Obstet., 120:975, 1965.
4. Crile, G.: A Biological Consideration of Treatment of Breast Cancer. Am. J. Surg., 109:400, 1967.
5. Donegan, W. L.: An Evaluation of Radical Mastectomy Following Simple Mastectomy for Cancer of the Breast. Mo. Med., 61:104, 1964.
6. Donegan, W. L., Perez-Mesa, C. M. and Watson, F. R.: A Biostatistical Study of Locally Recurrent Breast Cancer. Surg. Gynecol. Obstet., 122:529.
7. Farrow, J. H.: Resume of Standard Surgical Procedures at Memorial Hospital. Cancer, 23:1044, 1966.
8. Farrow, J. H., Fracchia, A. A., Robbins, G. F. and Castro, E.: Simple Excision or Biopsy Plus Radiation Therapy as the Primary Treatment for Potentially Curable Cancer of the Breast. Cancer, 28:1195, 1971.
9. Flores, L., Arlen, M. and Livingston, S.: Medullary Carcinoma of the Breast. (Submitted for publication.)
10. Haagenson, C. D. and Miller, E.: Is Radical Mastectomy Optimal Procedure for Early Breast Carcinoma. JAMA, 199:739, 1967.
11. Haagenson, C. D. and Cooley, E.: Radical Mastectomy for Mammary Carcinoma. Ann. Surg., 170:884, 1969.
12. Handley, R. S.: The Early Spread of Breast Carcinoma and its Bearing on Operative Treatment. Br. J. Surg., 51: 206, 1964.
13. Handley, R. S. and Thackray, A. C.: Conservative Radical Mastectomy (Patey's Operation). Ann. Surg., 170:880, 1969.
14. Kaae, S. and Johansen, H.: Simple Mastectomy Plus Postoperative Radiation by the Method of McWhirter for Mammary Carcinoma. *In* Progress in Clinical Cancer. Ariel, I. M., editor, New York, Grune and Stratton, 453, 1965.
15. Leak, G. H., Berg., J., West, E. H. and Robbins, G. F.: Primary Treatment of Patients with Resectable Breast Cancer. Surg. Gynecol. Obstet., 129:953, 1969.
16. Lewison, E. F., Montague, A. C. W. and Kullero, L.: Breast Cancer Treated at the Johns Hopkins Hospital, 1951–1956. Cancer, 19: 1359, 1966.
17. Margottini, M. and Bucalossi, P: Oncologia, 23: 70, 1949.
18. McWhirter, R.: Cancer of the Breast. Am. J. Roentgenol. Radium Ther. Nucl. Med., 62:335, 1949.
19. Risanen, P. M.: A Comparison of Conservative and Radical Surgery Combined with Radiotherapy in the Treatment of Stage I Carcinoma of the Breast. Br. J. Radiol., 423, 1969.
20. Robbins, G. F. and Urban, J. A.: Axillary and Internal Mammary Lymph Nodes in Patients with Potentially Curable Breast Cancer. Clinical Bulletin Memorial Sloan-Kettering Cancer Center. 1:127, 1971.
21. Silverberg, S. G., Chitale, A. R., Hand, A. D., Frazier, A. B. and Levitt, S. H.: Sinus Histiocytosis and Mammary Carcinoma. Cancer, 26:1177, 1970.
22. Smithers, D. W.: Cancer of the Breast. Brit. Inst. Radiology, 1952, 76–77, supp. 4.
23. Stender, H. S. and Kunitsch, G.: Die Strahlenbehandling des mammacarcinoms. Chirg., 39:263, 1968.
24. Turner-Warwick, R. T.: Lymphatics of the Breast. Brit. J. Surg., 46:574, 1969.
25. Urban, J. A. and Baker, H. W.: Radical Mastectomy with En-bloc En-continuity Resection of the Internal Lymph Node Chain. Cancer, 5:992, 1952.
26. Urban, J. A. and Massord, A. M.: Significance of Internal Mammary Lymph Node Metastases in Breast Cancer. Am. J. Roentgenol. Radium Ther. Nucl. Med., 3:130, 1971.
27. Urban, J. A. and Castro, E. B.: Selecting Variations in Extent of Surgical Procedure for Breast Cancer. Cancer, 28:1615, 1971.
28. Veronesi, U. and Zingo, L.: Extended Mastectomy for Cancer of the Breast. Cancer, 20:677, 1967.
29. Wangensteen, O. H., and Lewis, F. J. and Arhelgar, S. W.: The Extended or Superradical Mastectomy for Carcinoma of the Breast. Surg. Clin. North Am., 36:1051, 1956.

A New Complication of Subclavian Vein Catheterization

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AIR EMBOLISM OCCURRING THROUGH THE TRACT of an intravenous catheter leading from the skin below the right clavicle into the subclavian vein shortly after its withdrawal on the 14th day was recently documented by X-ray in a 15-year-old boy with Crohn's disease. While not immediately fatal, the effort to support the patient included the placement of another catheter by the supraclavicular approach to the right subclavian vein which was shown at autopsy to have transfixed the vein and extended into the pleural cavity where 2,000 ccs. of blood and fluid were found. While hemothorax has previously been documented following attempts to enter a subclavian vein, we are not aware that an air embolism occurring after removal of the subclavian catheter has previously been encountered.

Since Aubaniac[1] first described the percutaneous approach to the subclavian vein in 1952, catheterization of this vessel has become popular. Two forces have been responsible for this, the first being awareness of the value of central venous pressure monitoring and the second being the value of parenteral hyperalimentation in humans as shown by Wilmore and Dudrick[7] in 1968. Numerous reports have appeared in literature discussing the complications of the procedure, and hemothorax, pneumothorax, subcutaneous emphysema, hydrothorax, air embolism upon insertion, infection, thrombophlebitis, and hemotomas have all been well documented.

The technique of percutaneous subclavian vein catheterization has been in use at Pennsylvania Hospital since 1965. In that time, over 2,000 catheterizations have been performed. Similar complications, as those stated above, have been experienced at this institution. However, the morbidity from the procedure has been low, and the diagnostic and therapeutic gains have been so high that the procedure has become more frequently used. Our recent experience with one patient in whom two new complications secondary to subclavian vein catheterization occurred is the basis of this report.

Case Report

K. H., a 15-year-old black male, was admitted to Pennsylvania Hospital with the chief complaint of painful sores in the mouth. The patient had had frequent exacerbations of transmural colitis for the past three years with intermittent bouts of diarrhea, weight loss, and perirectal abscesses and fistulae formation. For three months prior to this admission he had been treated with large doses of steroids (60 mg. of prednisone daily) and salicylazosulfapyridine to try to effect a remission. Despite this treatment, remission did not occur and, in fact, the patient developed multiple oral abscesses probably as a complication of the steroid therapy. For this reason he was admitted to Pennsylvania Hospital and total abdominal colectomy was planned.

Because the patient was cachectic on admission, a six-week course of parenteral hyperalimentation was planned. The hyperalimentation fluid was administered through a catheter placed in the superior vena cava via the subclavian vein. Ten days after admission, while being treated in this fashion, he developed signs and symptoms of an acute abdomen and an exploratory laparotomy was performed.

At the time of laparotomy, a large pelvic abscess with diffuse purulent peritonitis was present, although no definite site of perforation could be observed in the colon. Total abdominal colectomy was performed and an end-ileostomy was created. The rectum was oversewn as a Hartmann's pouch.

Postoperatively he was dramatically improved until the fourth day when he became febrile. The fever appeared to be secondary to a wound infection. However, since the subclavian intercath had been in place for 14 days it was removed and the tip was cultured. One-half hour following removal of the subclavian catheter, the patient was sent to the Radiology Department for

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chest films. He was transported in the erect position sitting in a wheel chair. Upon arrival at the Radiology Department, he was noted to be diaphoretic and dyspneic. Chest X-ray performed at that time revealed air in the pulmonary outflow tract with decreased vascular markings at the apices of both lung fields (Fig. 1). While still in the Radiology Department, another film was taken which showed cardiac enlargement, but the air that was previously present in the pulmonary outflow tract was now gone. The patient was immediately returned to the Intensive Care Unit and once again was tachypneic and at that time hypotension and tachycardia were present. The patient responded to the administration of large volumes of fluid; however, a third chest X-ray revealed a picture consistent with interstitial pulmonary edema. The patient was treated with salt-poor albumin, lasix and digoxin; there was favorable response to this therapy. About an hour later another subclavian was placed, this time by the supraclavicular route. One-half hour following this, the patient once again became tachypneic and was hypotensive and had a tachycardia. Shortly after that the patient arrested and resuscitation efforts were unsuccessful.

At postmortem examination air was demonstrated to be present in the pulmonary outflow tract. A patent tract was identified leading from the skin to the subclavian vain. This was the site of the initial subclavian vein catheter which had been in place for 14 days. Two thousand ccs. of fresh blood were found in the right pleural space. A hole was found in the subclavian vein on the right side in its intrathoracic portion; an intercath was still in place and was protruding through this hole.

Discussion

The proof of the effectiveness of both intravenous hyperalimentation and central venous pressure monitoring have been the great impetus to the popularization of subclavian vein catheterization. Aubaniac[1] first described the procedure in 1952 and demonstrated its usefulness as a route for administration of intravenous fluids and for withdrawing blood for laboratory sampling in patients in whom other veins were not available. It did not gain popularity in this country until 1962 when Wilson[8] showed that central venous pressure monitoring played a key role in the management of critically ill patients and at that time described a modified technique for percutaneous catheterization. In 1968, when Wilmore and Dudrick[7] showed that with only intravenous feeding solutions adequate nutrition and normal growth could be achieved in humans, subclavian vein catheterization became even more popular. Since that time multiple reports have appeared in the literature describing both alternate techniques and complications of the procedure.

In 1965, Yoffa *et al.*[10] advocated the supraclavicular approach to the vein. They felt that this approach was easier and demonstrated that there was no evidence of hematomas or pneumothoraces in any of their patients. They achieved entrance into the vein in 80% of cases on the first try, and out of 130 veni-punctures only failed to enter the vein in five cases. They pointed out that patients should be kept in the recumbent position so that the vein will be fuller and therefore easier to enter and also that the risk of air embolus will be diminished. In 1970, Johnson *et al.*[5] reported a case of air embolism during the introduction of the catheter into the vein. This patient was in a hypovolemic state. Flanagan *et al.*[3] in 1969 also reported a case of air embolism secondary to this procedure. The patient in this case was in the semi-Fowler position and had a low central venous pressure. These authors, using a modification of Poiseuille's Law, calculated that with a 14-gauge needle, whose internal diameter is .072 inches, 100 ccs. of air per second could be transmitted, if there were a pressure drop of 5 cm. of water. They also experimentally showed that volumes of air of this magnitude rapidly administered intravenously to dogs altered cardiopulmonary physiology. Though the minimal volume of air lethal to human beings has not yet been clearly demonstrated, Yaedel[9] in 1968 reported that 100 ccs. of air which was rapidly forced through the vascular system from a classic blood storage container caused a fatal air embolus. Gallitano *et al.*[4] in 1972 advocated the infraclavicular route for subclavian vein catheterization. They reported on over 600 cases with no morbidity or mortality. In ten per cent of the cases they were unable to cannulate the vein and did not persist. They felt that persistence in cannulating the vein led to complications. They advocate its use by a wider number of people in all hospitals. Bernard *et al.*[2] undertook an interesting study in which they did a pros-

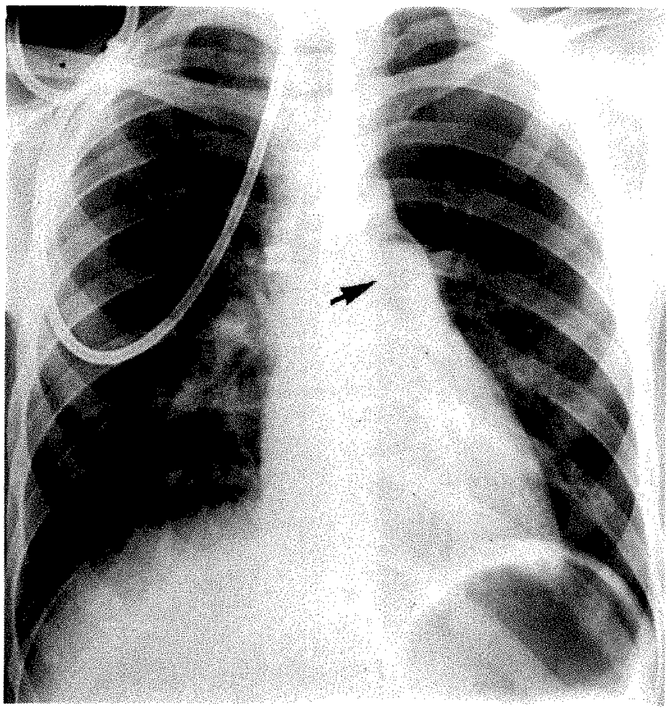

FIG. 1. Chest X-ray demonstrating air in the pulmonary outflow tract marked by black arrows and decreased vascular markings at the apices of both lung fields.

pective analysis of complications of subclavian vein catheterization and found that there was an inverse correlation between the experience of the physician inserting the catheter and complications. Their overall complication rate was 4.5%; they used a modification of Dudrick's technique for the infraclavicular approach.

The case presented here demonstrates two complications from subclavian vein catheterization. The fatal event was secondary to hemorrhage through the intrathoracic portion of the subclavian vein. This catheterization was attempted by the supraclavicular route. This is an avoidable complication. It has been stressed that when entering the vein from the superior approach, the operator must be extremely careful not to introduce the needle too far.

The complication of air embolus through a subclavian vein catheterization tract after removal of the catheter has not been reported. We postulate that shortly after removal of the catheter which was filled with solution, air entered the central venous system through the catheter tract. Air was evident in the pulmonary outflow tract on a chest X-ray performed shortly thereafter.

Most patients in whom subclavian vein catheters are in place for a short period of time will probably not develop a fibrous tract around the catheter. We feel the complication of air embolus after removal will arise in patients who have had a catheter placed for a prolonged period of time and therefore would most likely occur in those patients receiving intravenous alimentation. Such patients may, in addition, present with muscle wasting and a decrease of subcutaneous fat tissue, both of which may contribute to the embolization via a tract by diminishing the distance between the skin and subclavian vein.

Our recommendation is that in all patients in whom the catheter has been in place long enough for a tract to develop, in any patient receiving hyperalimentation solution and in any patient who has muscle wasting and subcutaneous tissue lost, the needle wounds should be treated as capable of sucking air upon removal of the catheter. This is especially the case if the central venous pressure is in the low normal range. This complication can be prevented by covering the entrance wound with a vaselinized gauze pad, which should be left in place long enough for obliteration of the tract. Though in this particular case the air embolism was not immediately fatal, it did lead to serious complications and quite obviously could have been fatal.

Summary

A case is presented of a 15-year-old boy who sustained an air embolism following the removal of a subclavian vein catheter. The air embolism occurred via the tract left from the subclavian vein catheter. The patient also sustained a second complication of subclavian vein catheterization, that being massive hemothorax from a supraclavicularly placed subclavian vein catheter. This occurred secondary to the catheter transfixing the vein and allowing massive bleeding into the right hemithorax. References are made to various complications of subclavian vein catheterization and evidence is presented to substantiate the air embolism in this case. Though the air embolism was not immediately fatal, it led to hemodynamic alterations. Vaselinized gauze placed on the punctured site when the catheter is removed will prevent the complication of air embolism.

References

1. Aubaniac, L.: L'Injection Intra Veineuse Sous-claviculaire; Avantages et Technique. Presse Med., **60**:1456, 1952.
2. Bernard, R. W., Stahl, W. M.: Subclavian Vein Catherizations: A Prospective Study—Non-infectious Complications. Ann. Surg., **173**:184, 1972.
3. Flanagan, J. P., Gradian, I. A., Gross, R. J., *et al:* Air Embolus—A Lethal Complication of Subclavian Veinpuncture. N. Engl. J. Med., **281**:488, 1969.
4. Gallitano, A. L., Kondi, E. S. and Deckers, P. J.: A Safe Approach to the Subclavian Vein. Surg. Gynecol., Obstet., **135**:96, 1972.
5. Johnson, C. L., Laxarchick, J. and Lynn, H. B.: Subclavian Vena Puncture: Preventable Complications: Report of Two Cases. Mayo Clinic Proc., **45**:712, 1970.
6. Lefrak, E. A. and Noon, G. P.: Management of Arterial Injury Secondary to Attempted Subclavian Vein Catherization. Ann. Thorac. Surg., **14**: 294, 1972.
7. Wilmore, D. W. and Dudrick, S. J.: Growth and Development of an Infant Receiving All Nutrients Exclusively by Vein. JAMA, **203**:140, 1968.
8. Wilson, J. N., Grow, J. B., Demong, C. V., *et al.:* Central Venous Pressure in Optimal Blood Volume Maintenance. Arch. Surg., **85**:563, 1962.
9. Yaekel, A. E.: Lethal Air Embolism from Plastic Blood Storage Container. JAMA, **204**:267, 1968.
10. Yoffa, D.: Supraclavicular Subclavian Vena Puncture and Catheterization. Lancet, **2**:614, 1965.

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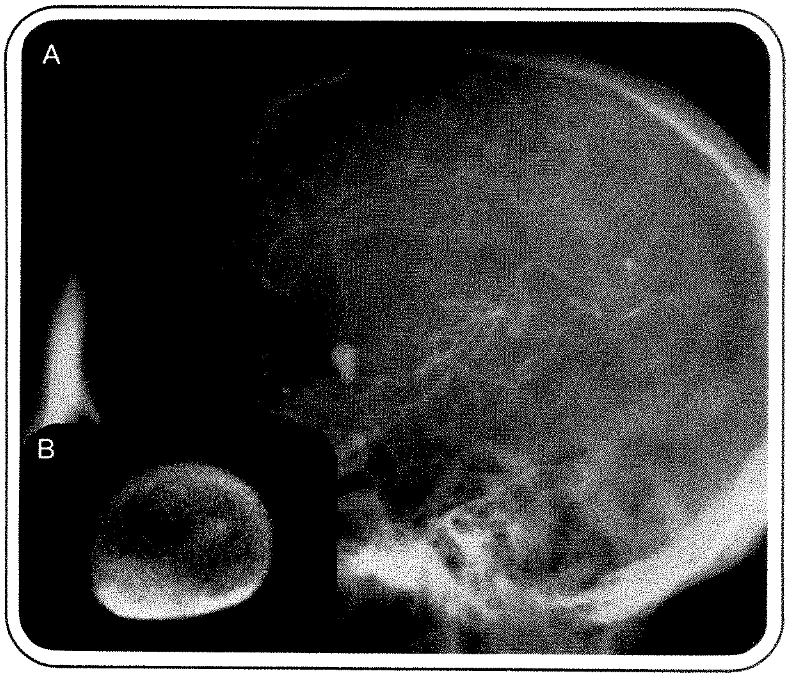

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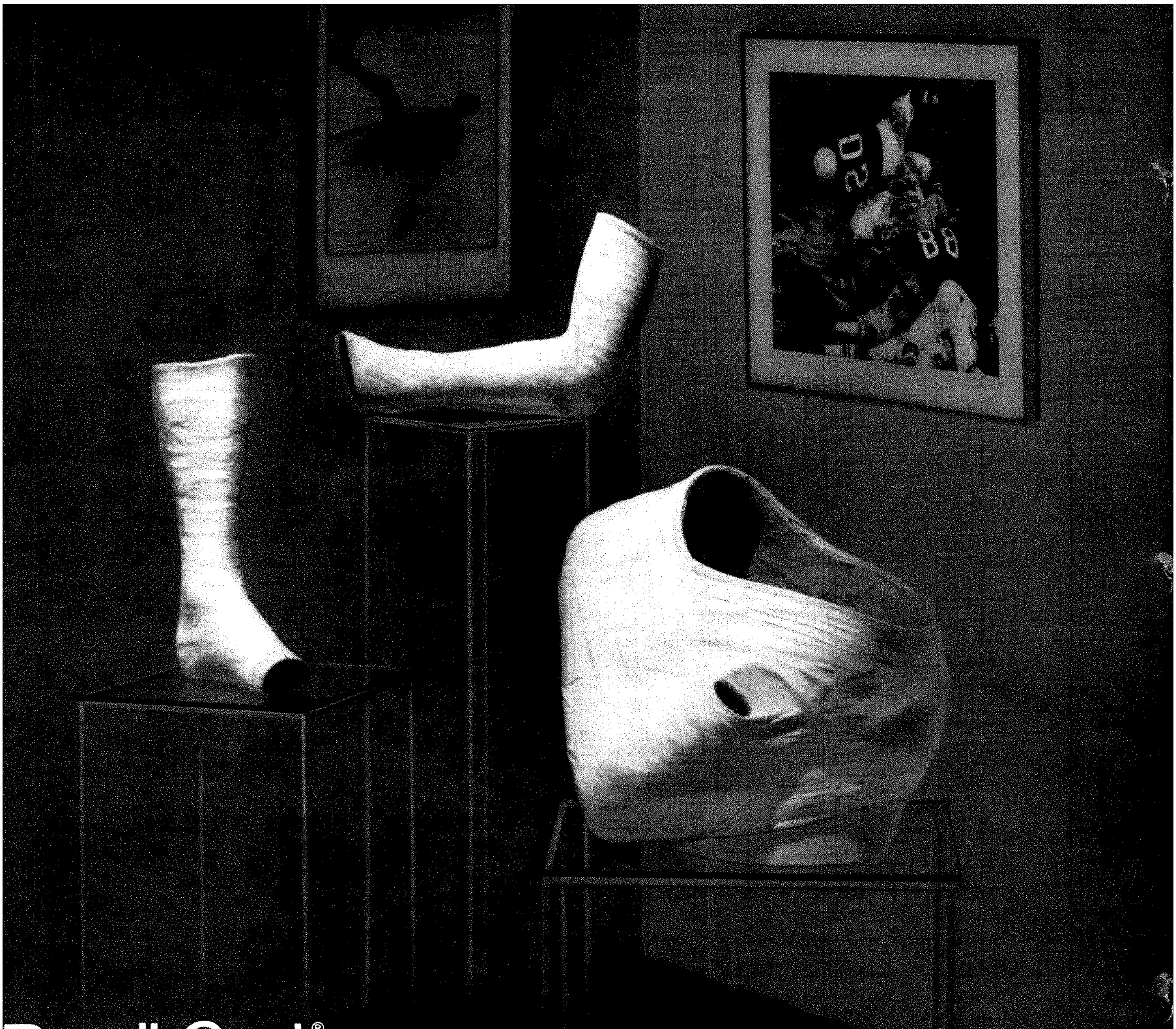

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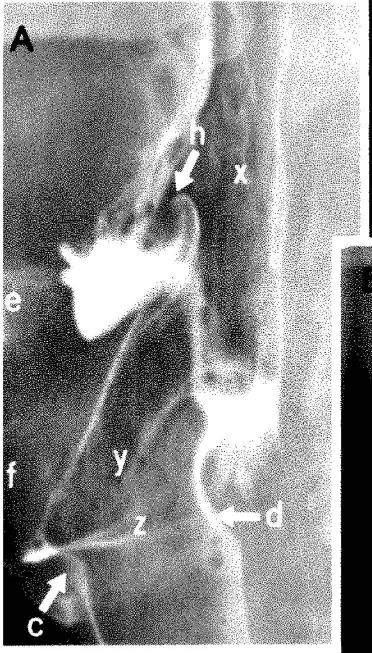
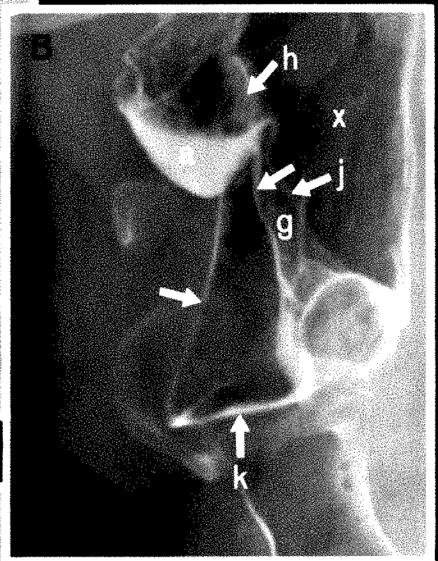
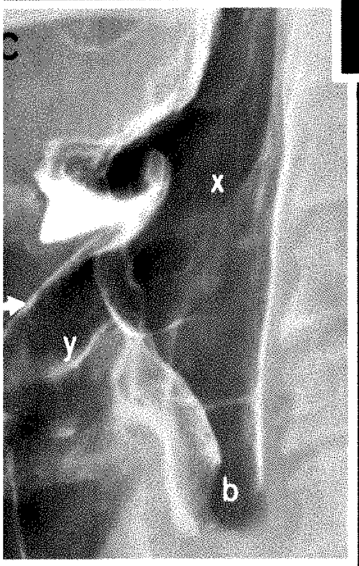


Figure I—Normal Laryngogram.

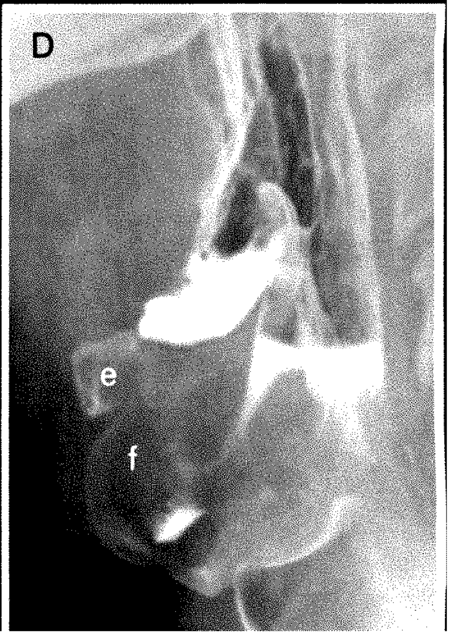
A. Quiet Breathing: Oropharynx (x); laryngeal vestibule in hypopharynx (y); laryngeal ventricles in hypopharynx (z); valleculae (a); pyriform sinuses (b); anterior commissure (c); posterior commissure (d); hyoid bone (e); calcified thyroid cartilage (f); epiglottis (h).



B. Phonation: When the vowel "eee" is sounded at a high pitch, the oropharynx (x) becomes distended with air. The epiglottis (h) assumes a more vertical position billowing out the aryepiglottic fold (g) revealing its free margins (j). The slitlike laryngeal ventricle (k) may now be seen. Note the change in the configuration of the valleculae (a) and anterior wall of the laryngeal vestibule (arrow); the latter is now delicately curved toward the cervical vertebrae



C. Modified Valsalva: This is likened to blowing the trumpet with lips closed and cheeks fully expanded. Even greater distention of the oral pharynx (x) and laryngeal vestibule (y) develop with reversal of the gentle curve of the anterior wall of the latter (arrow). Note how well the pyriform sinuses (b) are now visualized. The hyoid bone (e) lies higher in the neck.



D. True Valsalva: As one strains against the closed glottis, the previously elevated hyoid bone (e) (seen in Fig. C) now descends to rest upon the thyroid cartilage (f). This is cogent evidence of normal

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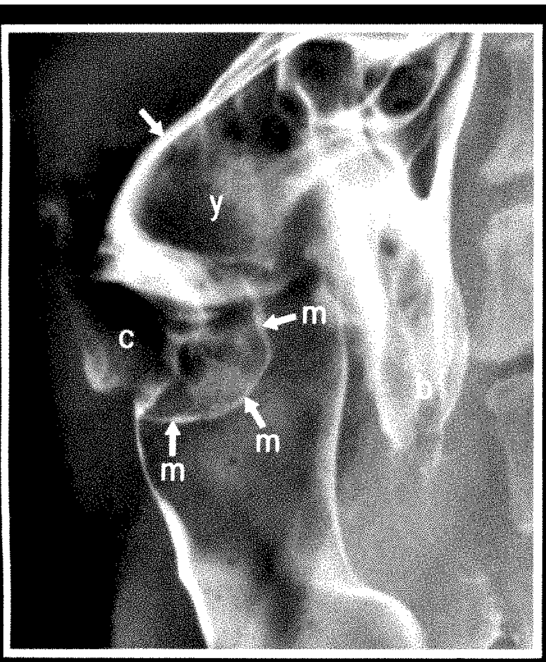
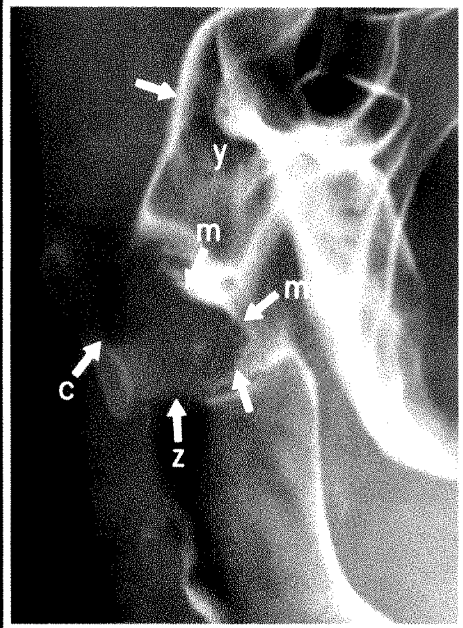


Figure II—Subglottic Tumor at Anterio Commissure.

Modified Valsalva: The laryngeal vestibul (y) is well distended and its anterior wal (arrow) bulges anteriorly as should be durin this maneuver. Note too, the distended pyr form sinuses (b). A large polypoid mass (m involves and extends below the anterior po tion of the laryngeal ventricle. Note total di ruption of the anterior commissure (c).

Figure III—True Vocal Cord Tumor with Marked Anterior Commissure Involvement.

Modified Valsalva: The opacified irregularly lobulated laryngeal mucosa (m) lies well behind the site of the normal anterior commissure (c). The anterior portion of the laryngeal ventricle (z) too has been destroyed. Most of the anterior wall (arrow) of the laryngeal vestibule (y) appears unaffected.



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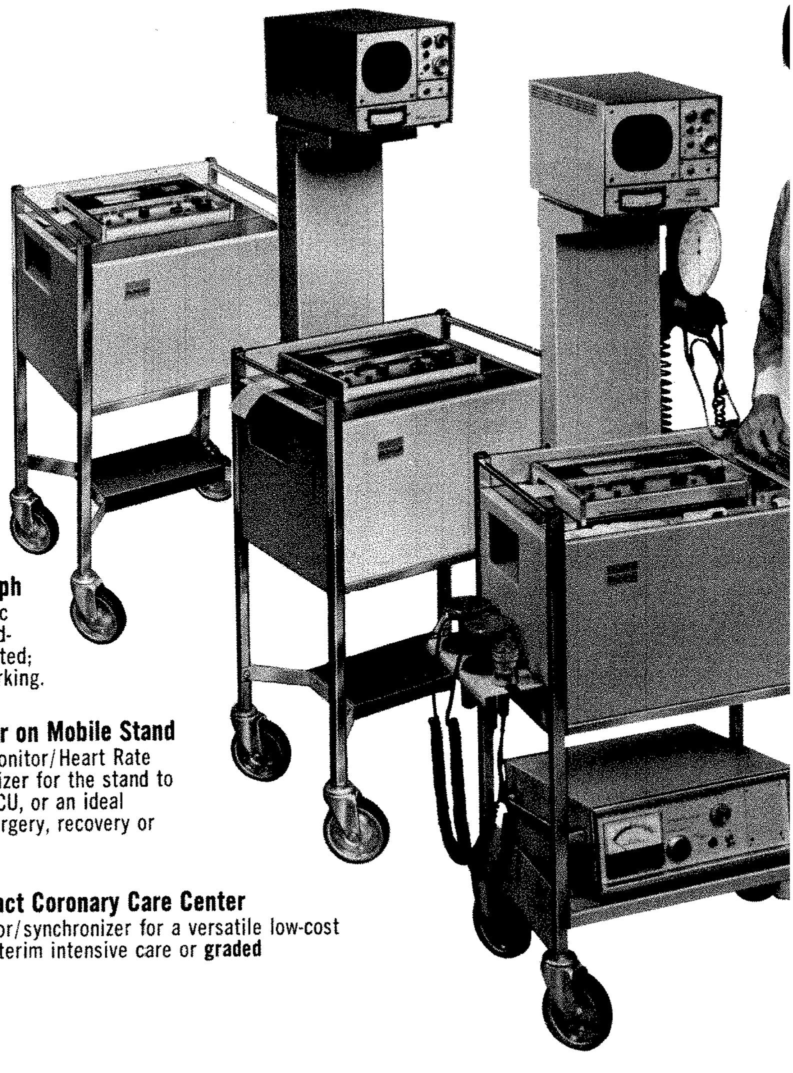

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Effectiveness of Axillary Lymph Node Dissection in Modified Radical Mastectomy with Preservation of Pectoral Muscles

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TODAY MANY SURGEONS ARE CONVINCED that axillary lymph node dissection is as complete in modified radical mastectomy as it is in the classical operation with removal of both pectoral muscles.[1,6-12]

The principal aim of the present study was to ascertain whether effective axillary lymph node dissection in fact could be achieved without sacrificing the pectoral muscles. It was considered particularly interesting to identify those axillary lymph nodes which were most likely to be overlooked and to determine whether such nodes belonged to the ones draining the breast. An evaluation of the regional lymph node drainage from the mammary gland has been published recently.[2,3] The roles of non-interpectoral lymph nodes on the dorsal aspect of the major pectoral muscle and of the interpectoral lymph nodes—of particular interest in this context—have also been dealt with specifically in a previous paper.[4] Accordingly, the present investigation will be confined to the axillary lymph nodes.

Materials

Seven women with clinical, roentgenological and cytological evidence of mammary carcinoma, but without clinical signs of metastases to the axillary lymph nodes, were chosen for a special operation in two sessions, which subsequently will be described in greater detail. Cases 1 and 2 in this series have been included in previous studies.[2,3] Prior to surgery a tracer substance (^{198}Au) was injected in the parenchyma of the breast, followed next day by injection of Lipiodol for lymphography.

Tracer Studies

A colloidal ^{198}Au suspension was injected with a fine-bore needle in amounts of 0.5–1.5 ml and 1.5–5.0 mCi (for details see reference 2).

Lymphographic Studies

Lymphography was performed by intralymphatic injection in the dorsum of the hand of 6–8 ml Lipiodol Ultra Fluide 38%. The procedure has been described fully.[2]

Operative Procedures

First Stage

A modified radical mastectomy with preservation of the pectoral muscles was performed on each patient. As the attitude of the surgeons involved might considerably affect the result, four technically highly skilled surgeons were asked to perform its first stage. Three were closely familiar with modified radical mastectomy and were convinced that complete axillary clearance could be achieved thereby. The fourth surgeon had used the operation routinely for a number of years but was unbiassed as regards its effectiveness in clearing the axilla. All four surgeons used the technique they were accustomed to.

In Cases 1, 2 and 3 the surgeon laterally divided the minor pectoral muscle at its attachment to the coracoid process; in Cases 4 and 5 the surgeon left the minor pectoral muscle unsevered; and in Cases 6 and 7 this muscle was divided at its attachment to the thoracic wall.

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TABLE 1. *Time Required for the Operative Procedures*

Case No.	1st Stage of Operation, i.e. Modified Radical Mastectomy	2nd Stage of Operation, i.e. Removal of Pectoral Muscles and Further Axillary node Dissection	Application of Permanent Suction and Closure of the Operative Wound
1	115 min.	25 min.	20 min.
2	100 min.	30 min.	12 min.
3	70 min.	48 min.	16 min.
4	120 min.	35 min.	18 min.
5	125 min.	51 min.	33 min.
6	85 min.	67 min.	38 min.
7	100 min.	100 min.	15 min.

Second Stage

When the first surgeon considered the operation satisfactory, a second senior surgeon took over and completed the operation by removing the pectoral muscles and fasciae, thus converting the operation to a standard radical mastectomy according to Halsted-Meyer. Any axillary lymph nodes previously overlooked were carefully searched for during the second session. Their anatomical locations were determined and they were collected for subsequent analysis (*vide infra*). The times elapsed during the performance of the various operative procedures were recorded and are set out in Table 1.

Postoperative Examination of Specimens

Specimens from both sessions of the operation were analyzed by roentgen examination, measurement of radioactivity, autoradiography and histological examination. All these procedures have been described elsewhere.[2] In the present context particular attention was paid to the specimen from the second stage of the operation.

Results

Though the majority of the axillary lymph nodes were removed at the first session of the intervention, in other words at the modified radical procedure (Table 2), a varying number (1–10) of lymph nodes were—the utmost care notwithstanding—overlooked. As appears from Table 3, the vast majority (29 of 33) of these lymph nodes, all removed at session II of the operation, belonged to the subclavicular group of axillary lymph nodes, *i.e.* those in the apex of the axilla; one was located in the central axillary region; three in the scapular region. None of the lymph nodes that had been missed at the first session of the operation was the site of a metastasis, as might have been expected from the fact that none of the patients exhibited either clinical or roentgenological signs of metastases to the axilla.

As appears from Table 4, ^{198}Au—the tracer preoperatively injected into the breast—was present in 23 of the 33 lymph nodes missed at the first stage of the operation. Presumably, therefore, these lymph nodes primarily were concerned in the lymphatic drainage of the breast. In comparing the two tables it becomes apparent that a substantial proportion of these lymph nodes belonged to the subclavicular group. Notably, however, in two patients only a single axillary lymph node could be found at the second stage of the operation, and neither ^{198}Au nor Lipiodol was present in these two nodes.

Discussion

It should be stated that the present study is but one in a series of recent papers devoted to the functional anatomy of the breast and its lymphatics. One of these

TABLE 2. *Axillary Lymph Nodes (lnn) Removed both at the 1st Stage (i.e. Modified Radical Mastectomy) and at the 2nd Stage of Operation (Thus Transforming the Operation to Halsteds Type of Radical Mastectomy)*

Case No.	Lnn Removed at the 1st Stage of Operation	Lnn Removed at the 2nd Stage of Operation (Overlooked lnn)	Total Number of Removed Axillary lnn	Lnn with both ^{198}Au and Lipiodol	Lnn with Only ^{198}Au	Lnn with only Lipiodol	Lnn without ^{198}Au and Lipiodol	Lnn Metastases
1	35	3	38	29	2	2	5	0
2	58	7	65	59	5	0	1	3
3	31	4	35	18	13	1	3	0
4	24	1	25	23	0	0	2	0
5	35	1	36	24	2	9	1	0
6	28	7	35	25	2	5	3	0
7	20	10	30	12	6	5	7	0
Total	231	33	264	190	30	22	22	3

TABLE 3. *Incidence and Location of Axillary Lymph Nodes (lnn) Overlooked at Modified Radical Mastectomy*

Case No.	Total Number of Axillary lnn	Number of Overlooked lnn	Location (Group) of Overlooked lnn
1	38	3	All subclavicular
2	65	7	All subclavicular
3	35	4	Three subclavicular, one scapular
4	25	1	Subclavicular
5	36	1	Central
6	35	7	Five subclavicular, two scapular
7	30	10	All subclavicular
Total	264	33	Subclavicular 29 Central 1 Scapular 3

papers clearly demonstrated that most axillary lymph nodes serve two regions of lymphatic drainage: the arm and the breast.[3] It was considered most unlikely that lymph nodes within these regions could drain to separate groups of axillary nodes, and from surgical points of view it was stressed that radical treatment of breast carcinoma requires removal of every lymph node in the axilla. Another investigation[4] revealed strong evidence that breast cancer also might spread through the deep fascial plane and the pectoral muscles to lymph nodes on the dorsal surface of the latter. Preservation of these muscles would thus seem to be hazardous in the treatment of breast cancer.

The present findings further support the view that complete axillary lymph node dissection is impossible to attain without sacrificing the pectoral muscles. This is at variance with the belief of most previous workers. For example, Madden *et al.*[6] used lymphographic methods to prove complete clearance of the axilla. Roentgen examination was used merely to check the removal of contrast-filled lymph nodes. The authors apparently were unaware that some lymph nodes might be overlooked owing to incomplete or absent contrast filling, something that might arise as a result of metastatic involvement.[5] Only patients without clinical and roentgenological evidence of axillary lymph node metastases were chosen for the present investigation. Hence abnormal contrast filling of lymph nodes and/or deviant lymph flow could be ruled out in all but a single case. More reliable identification of the regional lymph nodes might be expected from the use of ^{198}Au injections into the mammary gland. It should be emphasized that a surprisingly large number of lymph nodes were missed, despite the fact that all the surgeons concerned had been fully informed about the second stage of the operation and therefore presumably would make every effort to clear the axilla.

It will be seen, therefore, that in all cases the modified procedure was ineffective in clearing the axillary lymph nodes. The majority of the lymph nodes that had been overlooked belonged to the subclavicular group and most of them also contained the radioactive tracer. In all probability, therefore, those lymph nodes which are susceptible to be missed at modified radical mastectomy are significant as regards the site of metastases and should be removed as well. This conclusion presupposes that regional lymphadenectomy contributes to the eradication of the disease. But the object of complete axillary lymph node dissection in breast cancer is not therapeutic only. Thorough and complete axillary clearance is essential also for the establishment of the histological stage of the disease. This, combined with clinical findings and the histology of the primary carcinoma, facilitates individualization of the postoperative irradiation programme.

Summary

In a study of the effectiveness in clearing axillary lymph nodes of modified radical mastectomy with preservation of the pectoral muscles, seven patients were examined by preoperative ^{198}Au injection into the breast parenchyma and lymphography via the lymphatics of the hand. The patients underwent a type of two-stage operation. The first stage was modified radical mastectomy with preservation of the pectoral muscles. The second stage, performed by a different surgeon, transformed the former operation to a standard radical mastectomy according to Halsted-Meyer, thus removing the pectoral muscles and any axillary lymph nodes overlooked by the first surgeon. The results strongly suggest

TABLE 4. *Tracer Contents in Lymph Nodes (lnn) Overlooked at Modified Radical Mastectomy (All lnn without Metastases)*

Case No.	Number of Overlooked lnn	Lnn with ^{198}Au and Lipiodol	Lnn with only ^{198}Au	Lnn with only Lipiodol	Lnn without ^{198}Au and Lipiodol
1	3	3	0	0	0
2	7	7	0	0	0
3	4	1	1	1	1
4	1	0	0	0	1
5	1	0	0	0	1
6	7	3	2	1	1
7	10	6	0	2	2
Total	33	20	3	4	6

that complete axillary lymph node dissection is a goal impossible of attainment without sacrificing the pectoral muscles.

References

1. Auchincloss, H.: Significance of Location and Number of of Axillary Metastases in Carcinoma of the Breast—A Justification for a Conservative Operation. Ann. Surg., **158**:37, 1963.
2. Hultborn, A., Hultén, L., Roos, B., Rosencrantz, M., Rosengren, B. and Åhrén, Chr.: Evaluation of Regional Lymph Drainage from Mammary Gland and Hand to Axillary Nodes. Acta Radiol. Ther. Phys. Biol., **9**:489, 1970.
3. Hultborn, A., Hultén, L., Roos, B., Rosencrantz, M., Rosengren, B. and Åhrén, Chr.: Topography of Lymph Drainage from Mammary Gland and Hand to Axillary Lymph Nodes. Acta Radiol. Ther. Phys. Biol., **10**:65, 1971.
4. Hultborn, A., Hultén, L., Roos, B., Rosencrantz, M., Rosengren, B. and Åhrén, Chr.: Lymphatic Spread of Mammary Carcinoma. Role of Non-interpectoral Lymph Nodes on Dorsal Surface of Pectoralis Major Muscle and of Interpectoral Nodes. Acta Radiol. Ther. Phys. Biol., **10**: 210, 1971.
5. Hultén, L., Åhrén, Chr. and Rosencrantz, M.: Lymphangioadenography in Carcinoma of the Breast. Comparative Clinical, Roentgen, and Histologic Appraisal of the Method for the Demonstration of Lymph-node Metastases. Acta Chir. Scand., **132**:261, 1966.
6. Madden, J. L.: Modified Radical Mastectomy. Surg., Gynecol. Obstet., **121**:1221, 1965.
7. Madden, J. L., Kandalaft, S. and Bourque, R.-A.: Modified Radical Mastectomy. Ann. Surg., **175**:624, 1972.
8. Patey, D. H. and Dyson, W. H.: The Prognosis of Carcinoma of the Breast in Relation to the Type of Operation Performed. Brit. J. Cancer, **2**:7, 1948.
9. Pickren, J. W., Rubé, J. and Auchincloss, H. Jr.: Modification of Conventional Radical Mastectomy. Cancer, **18**:942, 1965.
10. Rendall, M. and Patey, D. H.: Efficiency of Axillary Clearance in Operations for Carcinoma of the Breast. Brit. J. Surg., **52**:565, 1965.
11. Rosenqvist, H. and Erwald, R.: Bröstcanceroperationen. (The Breast Cancer Operation) (In Swedish). Opusc. med., **8**:36, 1963.
12. Rosenqvist, H.: Kirurgisk behandling av bröstcancer. (Surgery for Breast Cancer) (In Swedish). Läkartidningen, **63**: 1023, 1966.

The Use of the Sengstaken-Blakemore Tube for Immediate Control of Bleeding Esophageal Varices

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PORTOSYSTEMIC VENOUS SHUNTING is accepted as the best method for the definitive control of hemorrhage from esophageal varices. Most studies indicate that the operative mortality is substantially reduced if the procedure is performed electively after massive hemorrhage is controlled and blood volume has been replaced. This interval also allows for assessment and correction of liver function, fluid and electrolyte balance and coagulation mechanisms. Considerable attention has therefore been given to methods for the immediate control of bleeding to permit an appropriate interval between the patient's emergency admission to the hospital and the definitive operation.

A variety of methods for the emergency control of variceal bleeding are in current use. These include tamponade, administration of pressors, transesophageal ligation of varices and emergency portosystem shunting. Although Sengstaken-Blakemore balloon tamponade remains the most popular technique for the initial control of variceal bleeding, several reports[2–4,6,9,10,12–14,16] have described high failure rates in the attempt to arrest hemorrhage and high morbidity and mortality directly resulting from this tube.

We present a group of patients in whom the Sengstaken-Blakemore tube (SBT) has been an effective method of emergency control of bleeding. We describe methods to minimize the associated complications.

Material

Between 1965 and 1972, 47 patients underwent 50 portosystemic shunt procedures at The Mount Sinai Hospital (one patient had three shunts and another had two). Of these, 25 patients entered the hospital bleeding actively from esophageal varices and esophageal tamponade was used as the sole or initial method of emergency control of hemorrhage. This group of 25 patients constitutes the series presently reported.

The group consisted of 13 men and 12 women. The mean age was 49.8 years (range 16–69). All patients had proven bleeding esophageal varices with portal hypertension and intrinsic liver disease. The SBT was used 35 times in these 25 patients.

Of the 47 patients who eventually underwent shunting, the SBT was not used in 22 patients or in 24 preshunting hemorrhagic episodes (one patient had three shunting procedures). In four patients, tamponade was not instituted because the patient was uncooperative or because prompt emergency shunt was elected. Four patients had proven variceal bleeding in the recent past but were not actively bleeding at the time of this admission. In seven patients, the bleeding was not sufficiently severe to warrant the use of the SBT and, in nine patients the bleeding ceased spontaneously or after ice water lavage.

Technique

For balloon tamponade, the Davol® S.B. tube is used (Fig. 1). Prior to passage, patency of all lumens and intactness of both balloons is confirmed. Before insertion of the S.B. tube, the stomach is copiously lavaged with iced saline and emptied with an Ewald tube. Tracheal suction apparatus is available. The tube is well-lubricated and gently passed via the nasal route. The pharynx is not anesthetized. Passage is more easily accomplished by

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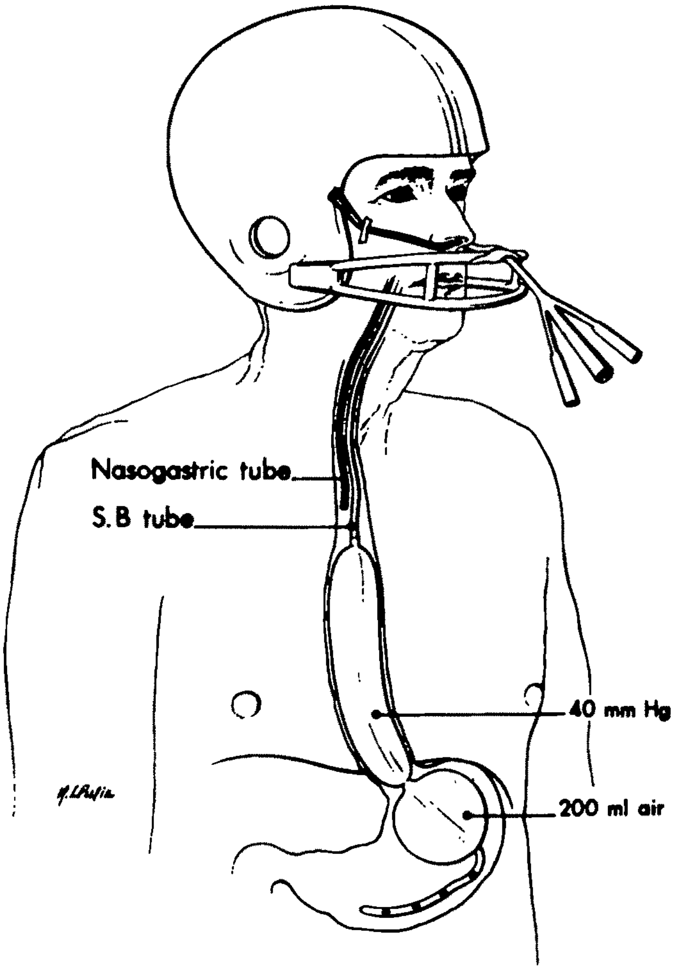

FIG. 1. The Sengstaken-Blakemore tube is in place with both balloons inflated. A nasogastric tube is placed through the contralateral external nares into a position just above the esophageal balloon.

having the patient slowly swallow some water. The tube is passed to 50 cm and the gastric balloon inflated with 200 ml of air and clamped. Very gentle traction is steadily applied until the gastric balloon is felt to be lodged at the gastroesophageal junction at which time the tube is taped to the face mask of a standard football helmet. The suction lumen is then irrigated and if bleeding has been controlled and the return from irrigation is clear, there is no need to inflate the esophageal balloon. If the bleeding is not controlled, the esophageal balloon is inflated to 40 mmHg. A small nasogastric tube is passed through the other external nares into the esophagus until it is felt to abut against the upper portion of the esophageal balloon. This is gently irrigated to check for bleeding and then attached to intermittent suction. If the bleeding is controlled, the patient is closely observed by the nursing and medical staff.

The tube, with both balloons inflated, is not disturbed for 24 hours, during which time adjunctive therapy and workup are instituted. Blood volume is restored, liver function, coagulation status and fluid and electrolyte status are assessed, and disorders corrected, if possible.

Because the residual blood in the gastrointestinal tract may provoke portosystemic encephalopathy, the colon is emptied by neomycin enemas, repeated until returns are clear. Cathartics are given via the tube. We prefer 30 ml doses of Fleets® phosphosoda. During this interval, intensive prophylactic respiratory therapy is instituted including nasothracheal suction, intermittent positive pressure breathing, and postural drainage.

If no further bleeding ensues during the first 24 hours, the esophageal balloon is deflated. The gastric balloon is deflated after another 24 hours and the tube is left in place on intermittent suction. If there is no further bleeding, the tube is removed after another 24 hours. If bleeding recurs at any time prior to removal of the tube, both balloons are quickly reinflated and consideration is given to prompt surgery.

Results

As shown in Fig. 2, the SBT was used to control hemorrhage in 25 patients. It successfully arrested the first hemorrhage in 21 of these patients. In the other four patients, emergency portosystemic shunts were performed. Of those in whom bleeding stopped, twelve did not rebleed after deflation of the baloons and had interval portosystemic shunts.

Nine patients rebled when the balloons were deflated. Of these, six were controlled by reinflation. In three patients, rebleeding was not controlled. These patients underwent emergency portosystemic shunt.

Of the six patients in whom rebleeding was controlled, five had complete control; one had partial control and underwent shunting several days later. One patient re-

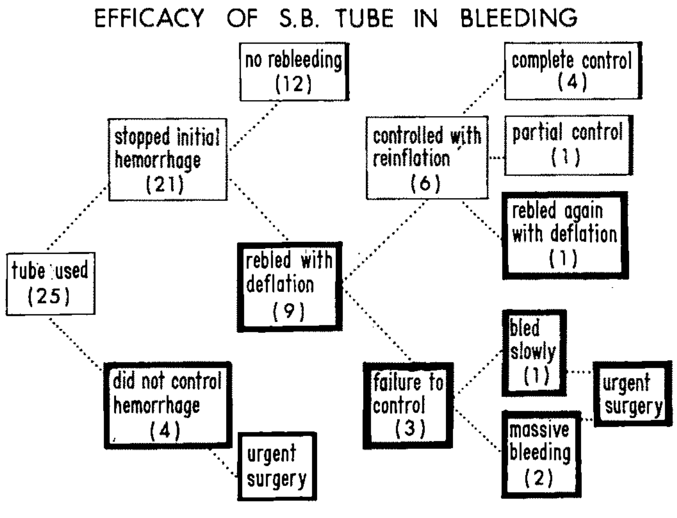
EFFICACY OF S.B. TUBE IN BLEEDING
tube used (25)
stopped initial hemorrhage (21)
did not control hemorrhage (4)
urgent surgery
no rebleeding (12)
rebled with deflation (9)
controlled with reinflation (6)
failure to control (3)
complete control (4)
partial control (1)
rebled again with deflation (1)
bled slowly (1)
massive bleeding (2)
urgent surgery

FIG. 2. Results of Sengstaken-Blakemore Tamponade in 25 patients.

bled again after a second attempt at deflation of the balloons and underwent emergency shunting.

Complications

Two deaths occurred:

In one patient, the gastric balloon ruptured during endotracheal intubation in the operating room. As a result, the tube slipped up the esophagus enabling the inflated esophageal balloon to occlude the airway causing transient hypoxia and then respiratory arrest. He was resuscitated and surgery was performed. However, he failed to regain consciousness after the operation and died two days postoperatively.

Case Report

One patient is briefly presented.

A 50-year-old male alcoholic with Laennec's cirrhosis and known esophageal varices presented with melena for one week and hematemesis for one day. The SBT was inserted and initially controlled bleeding, but the patient then developed a coagulopathy with a prothrombin time of 30/12 secs which could not be corrected in spite of administration of Vitamin K and fresh frozen plasma. An attempt was made to deflate the balloons several times, but each time the patient started to bleed moderately from the varices. After 5½ days with the balloons inflated and in place, the gastric balloon was again deflated. The patient bled massively and reinflation of the balloons did not control the bleeding. The patient underwent emergency portocaval shunt while actively bleeding and with the prothrombin time only partially corrected (24/12 sec). The patient continued to bleed postoperatively and expired on the first postoperative day. Necropsy revealed a patent portocaval anastomosis. There was a deep erosion in the wall of the distal esophagus measuring 5 × 3 cm and containing fresh clot at the base. No other bleeding was identified. It is assumed that the erosion was a direct result of pressure necrosis caused by the prolonged (5½ days) use of balloon tamponade.

In addition to two mortalities, there was one serious complication. A patient aspirated blood while the SB tube was being inserted. Endotracheal suction was rapidly instituted as was bronchial lavage but he still developed an aspiration pneumonia which responded to chest physiotherapy and antibiotics.

Discussion

The first reported case of control of variceal hemorrhage by tamponade was by Westphal[19] in 1930. In his report the varices were compressed by an esophageal sound. Since that time, several methods have been described. In 1950, Sengstaken and Blakemore[15] reported the technique of a double balloon tamponade, a method still widely used.

Early reports[3,6,9,14,16] described effective initial control of variceal hemorrhage in approximately 45–75% of the episodes. These observers also noted that if definitive operation was not undertaken following the initial control of bleeding, a large percentage of the patients rebled. Thus the definitive control of hemorrhage by balloon tamponade was only in the range of 24–50%.

Our results are similar to those previously reported. Twenty-eight of 35 (80%) bleeding episodes were controlled with Sengstaken-Blakemore tamponade. Twenty-one of 25 (84%) initial bleeding episodes were controlled by this method and of the nine patients who rebled after deflation of the balloons, six (67%) were controlled by reinflation.

It is our conviction that where possible, S.B. tamponade should be used to arrest hemorrhage and that definitive surgery should be performed after an interval; the results of elective portosystemic shunt have been shown by a majority of investigators to be better than those performed during active bleeding.

Some investigators[11,13] disagree with this approach, and propose that in selected patients, emergency portosystemic anastomosis provides the best chance of survival. They have found the relative effectiveness of the S.B. tube to be too low and the complications attributable to its use too high.

Thus there is general agreement that this method properly used, is an effective method to control bleeding; however, the complications that occur are often serious and may be fatal and because of this, many feel that its use should be limited.

The most common serious complications previously reported have been rupture or erosion of the esophagus[2–8,10,12,18,20] and occlusion of the airway by the balloon.[2–4,12,14,16] Conn[4] reported major complications in 35% of the patients in whom the tube was used, with nine deaths attributable to these complications (22%). Two deaths were a result of rupture of the esophagus. One death was caused by airway obstruction and six deaths were caused by regurgitation and aspiration of gastric contents. This author emphasized that because of the high complication rate, S.B. tamponade should be used only in "those critically ill patients in whom the higher risks attending its use are justified."[4]

In our group of twenty-five patients in whom S.B. tube was used 35 times, serious complications developed in three patients or 8.6% of the times the tube was used. In two (5.7%) of these instances, the complications proved fatal. One patient hemorrhaged from a deep distal esophageal erosion caused by the esophageal balloon. In the other who died, the gastric balloon ruptured during endotracheal intubation in the operating room enabling the esophageal balloon to slip up the esophagus and occlude the airway. The other serious complication was an aspiration pneumonia which responded to therapy. Our complication rate is similar to that of Hermann and Traub[8] who reported a series in which the SBT was used 109 times in 75 patients. The overall effectiveness of the SBT in arresting hemorrhage was 83.6%. Complications directly attributable to the tube occurred in 10 patients (9.2%) with 4 mortalities (3.7%). Three of the patients had aspiration pneumonia with resultant cardiorespiratory failure and death. We feel that our complication and mortality rates, closely paralleling that of Hermann and Traub, are acceptable in light of the poor general condition of the patients, the urgency of the situation, and the high mortality consequent upon emergency surgery.

Our series may be favorably weighted because only those patients who were seen by the surgical service and eventually underwent portosystemic anastomosis were reviewed; those patients who died before shunts could be performed or who were rejected for shunting because of excessively high risk were not included in the series.

We feel that close adherence to the described technique of S.B. tube insertion is important in minimizing complications. There are several points to be emphasized. The lower incidence of complications reported here is primarily attributable to fewer instances of aspiration of gastric contents either during, or subsequent to insertion. Six of the nine deaths reported by Conn[4] were secondary to aspiration. We employ several safeguards to avoid this complication. The pharynx is not anesthetized so that the gag reflex is intact. Nasotracheal suction is available. After the balloons have been inflated, a small (#12 french) nasogastric tube is inserted through the contralateral nares. This enables the staff to determine whether or not there are bleeding varices above the level of the esophageal balloon. This has occurred in two instances and in both cases the patients underwent emergency portocaval shunts. In addition, esophageal and pharyngeal secretions can be continuously suctioned. There is a commercially available four lumen tube manufactured by Davol® (model #9222) which contains a lumen designed to aspirate the esophagus above the esophageal balloon. In our experience, we have found this lumen to be too small to be completely effective and we prefer the previously described method of inserting a separate nasogastric tube into the esophagus above the esophageal balloon. We believe that this maneuver has enabled us to avoid the potentially lethal sequelae of aspiration.

One of the lethal complications in our series of patients and one which continues to be reported, is erosion of the esophagus. The erosion is probably a result of ischemic necrosis of the esophageal mucosa and can therefore be caused by excessive traction on the tube or prolongation of the length of time that the balloons are inflated. In our reported patient, the balloon was inflated for a total of 5½ days. Attempts at deflation were made several times but the patient continued to ooze slowly. This was complicated by a coagulopathy. Whenever possible, the esophageal balloon, in particular, should be deflated within 24 hours. If bleeding recurs after deflation, the balloon should be reinflated and if bleeding is controlled, the patient be prepared for surgery within the next 36–48 hours.

Airway occlusion by the esophageal balloon causing asphyxia has been reported rather frequently[2–4,12,14,16] and was responsible for one of the two deaths in our series of patients. This is usually caused by either sudden rupture or inadvertent slow deflation of the gastric balloon which then makes it possible for the esophageal balloon to slip proximally up the esophagus until it obstructs the airway either in the oropharynx or larynx. Complications such as these can be minimized by always using a new SBT which has been carefully checked by inflating all balloons before insertion of the tube. It has been suggested that bandage scissors should be tied to the SBT so that the tube can be instantly divided. This would allow the esophageal balloon to immediately deflate promptly reducing the obstruction to the airway.

Acute perforation of the esophagus by the inflated gastric balloon can be prevented by passing the tube to 50 cm before inflation to be certain that gastric balloon is in the stomach and not the esophagus.

Once the tube has been satisfactorily positioned, we have found the technique described by Wallace[17] to be valuable, i.e. to fix the tube to a rigid face mask. We use the faceguard of a standard football helmet. This enables us to maintain the gastric balloon impacted at the esophagogastric junction by constant, sustained, gentle traction. This assures proper position of the inflated esophageal balloon in the lower part of the esophagus.

In an attempt to avoid all of the previously mentioned complications of balloon tamponade, several investigators have attempted alternate methods for controlling hemorrhage from varices. Baum *et al.*[1] described a technique of selective angiography of the celiac and superior mesenteric arterial systems to diagnose and acutely localize the site of upper gastrointestinal hemorrhage. As an extension of their diagnostic studies, they discovered that infusion of dilute pitressin into the superior mesenteric artery could arrest bleeding from esophageal varices. The mechanism is presumed to be vasoconstriction of the arterial splanchnic bed, resulting in a decreased arterial inflow and hence a decrease in splanchnic venous outflow with concomitant reduction in portal venous pressure. They reported a series of 13 pts. with effective arrest of hemorrhage in 12 cases.

Our own experience using this technique is limited to a few selected cases with encouraging results. We are concerned about the dangers of sustained arterial vasoconstriction to segments of the gastrointestinal tract especially the intestine and a diseased liver. We have also been reluctant to use vasoconstrictors in those patients with coexistent coronary artery disease although Baum[1] reported no coronary complications.

An additional limitation of the technique of angiographic diagnosis and sustained vasopressor infusion is the need for an immediately available and skilled angiography team.

Nonetheless, we intend to expand our experience with this technique.

Summary

1. A series of 35 applications of the Sengstaken-Blakemore tube to control bleeding from esophageal varices in 25 patients is described.
2. The tube successfully arrested hemorrhage in 21 of 25 patients.
3. There were two fatalities directly attributable to the S.B. tube. One was caused by erosion of the distal esophagus and the other a result of airway obstruction by the balloon.
4. Only one major pulmonary complication occurred in this series of patients.
5. Techniques to minimize complications from the tube are described in detail. These include controlled placement of the S.B. tube without topical pharyngeal anesthesia, insufflation of the gastric balloon with 200 ml of air, and impaction of the gastric balloon at the cardioesophageal junction with sustained traction. In addition, a nasogastric tube is placed above the esophageal balloon for continuous aspiration of accumulated nasopharyngeal secretions.
6. It is emphasized that balloon tamponade should be used for a limited period of time, i.e. 48 hours.

With proper application of the Sengstaken-Blakemore tube, most acutely bleeding esophageal varices can be controlled. This permits subsequent portosystemic shunting to be performed under elective rather than emergency circumstances.

References

1. Baum, S., Nusbaum, M. and Tumen, H. J.: The control of Gastrointestinal Hemorrhage by Selective Mesenteric Infusion of Pitressin. Gastroenterology, **58**:926, 1970.
2. Bennet, H. D., Baker, L. and Baker, L. A.: Complications in the Use of Esophageal Compression Balloons (Sengstaken Tube). Arch. Int. Med., **90**:196, 1952.
3. Conn, H. O.: Hazards Attending the Use of Esophageal Tamponade. N. Engl. J. Med., **259**:701, 1958.
4. Conn, H. O. and Simpson, J. A.: Excessive Mortality Associated With Balloon Tamponade of Bleeding Varices. JAMA, **202**:135, 1967.
5. Francis, P. N., Perkins, H. W. and Pain, M. C. F.: Rupture of the Oesophagus Following Use of the Sengstaken-Blakemore Tube. Med. J. Aust., **50**:582, 1963.
6. Gow, G. A. and McGregor, O. D.: Hemorrhage From Esophageal Varices. Canad. Med. Assn. J., **83**:1032, 1960.
7. Hamilton, J. E.: Management of Bleeding Esophageal Varices. Ann. Surg., **141**:637, 1955.
8. Hermann, R. E. and Traul, D.: Experience with the Sengstaken-Blakemore Tube for Bleeding Esophageal Varices. Surg. Gynecol. Obstet., **130**:879, 1970.
9. Ludlington, L. G.: A study of 158 Cases of Esophageal Varices. Surg. Gynecol. Obstet., **106**:519, 1958.
10. Merigan, T. C. Jr., Hollister, R. M., Gryska, P. F., Starkey, G. W. G. and Davidson, C. S.: Gastrointestinal Bleeding with Cirrhosis: Study of 172 Episodes in 158 Patients. N. Engl. J. Med., **263**:579, 1960.
11. Mikkelsen, W. R.: Emergency Portocaval Shunt, Rev. Surg., **19**:141, 1962.
12. Orloff, M. J.: Comparative Study of Emergency Transesophageal Ligation and Nonsurgical Treatment of Bleeding Esophageal Varices in Unselected Patients with Cirrhosis. Surgery, **52**:103, 1962.
13. Orloff, M. J.: Emergency Portocaval Shunt: A Comparative Study of Shunt, Varix Ligation and Nonsurgical Treatment of Bleeding Esophageal Varices in Unselected Patients with Cirrhosis. Ann. Surg., **166**:456, 1967.
14. Read, A. E. et al.: Bleeding Oesophageal Varices Treated by Oesophageal Compression Tube. Brit. Med. J. **1**:227, 1960.
15. Sengstaken, R. W. and Blakemore, A. H.: Balloon Tamponage for the Control of Hemorrhage from Esophageal Varices. Ann. Surg. 131:781, 1950.
16. Telfer, B. et al.: Results of Treatment of Bleeding Esophageal Varices With Balloon Tamponade. Am. J. Med. Sci., **224**: 500, 1952.
17. Wallace, A., Wallace, W. B. and Balfour, D. C.: Use of a Head Mask to Aid in Esophageal Tamponage Gastroent. **24**:20, 1953.
18. Welch, C. S. et al.: Treatment of Bleeding from Portal Hypertension in Patients with Cirrhosis of the Liver. N. Engl. J. Med., **254**:493, 1956.
19. Westphal, K.: Veber eine Kompressionsbehandlung der Blutungen aus Oesophagusvarizen. Datsch Med Wschr, **56**: 1135, 1930.
20. Zeid, S. S., Young, P. C. and Reeves, J. T.: Rupture of the Esophagus After Introduction of the Sengstaken-Blakemore Tube. Gastroenterology, **36**:128, 1959.

The Epidemiology of Lower Extremity Deep Venous Thrombosis in Surgical Patients

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LOWER EXTREMITY DEEP VENOUS THROMBOSIS is considered to be a serious hazard in the course of patients undergoing surgical operations. A number of reports peak of the increased occurrence of venous thrombosis[3,6,10,12,15,18,21] and pulmonary embolism[6,12,15,21] in patients undergoing operations and attention has been directed at conditions which seem associated with these occurrences.[2,5,7,12,13,15,22] However, there are marked differences in the reported frequency of venous thrombosis.[4] It has been difficult to identify significant predisposing or associated conditions since these conditions are usually present in multiple combinations. Furthermore, it is generally recognized that the clinical methods for the diagnosis of venous thrombosis[8,19] and pulmonary embolism[20] pose serious problems in accuracy which probably accounts for some of the variability of reported results and their disparity with other diagnostic methods[11,29] and with postmortem findings.[8,14]

With these considerations in mind, we have performed a prospective epidemiologic study in patients undergoing elective surgery employing simultaneously two methods for diagnosing lower extremity deep venous thrombosis. The two methods were physical examination and Doppler ultrasound examination of the lower limbs. The study was designed to consider specifically and to relate the following aspects of the epidemiology of venous thromboembolic disease:

1. Prevalence of already existing venous thrombosis in patients coming to operation.
2. Incidence or rate of development of thrombosis in previously unaffected patients during the post-operative period.
3. Association of diagnosed venous thrombosis with clinically detected pulmonary embolism in the post-operative period.
4. Identification of risk factors associated with the presence of venous thrombosis pre-operatively (prevalence) and the occurrence of new thrombosis post-operatively (incidence).

This paper describes the methodology and presents the results of this study of 2877 patients undergoing elective surgical operations.

Methodology

The study was performed between January 1969 and September 1971 at the Hospital of the Medical College of Pennsylvania and the Veterans Administration Hospital in Philadelphia. All patients admitted to the general and thoracic surgical, orthopedic, neurosurgical, urologic, and gynecologic services were included. The consent and cooperation of the surgeons at these two hospitals was obtained and patients for study were selected from the operating room schedule for elective operations which usually appeared about noon of the day preceding operation. Consent of the patients was obtained prior to each examination and each examination was performed at the bedside by a nurse or technician.

Initial Examination

At the first visit to a patient on the day prior to operation, demographic and historical information was ob-

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tained from the patient, the chart, and the surgeon.

The physical and ultrasound examinations were performed at the bedside. The condition of the legs, particularly in regard to pitting edema, hyperpigmentation, ulcers or ulcer scarring, were noted. Circumference measurements were recorded at three symmetrical sites on each extremity: 1) five inches above the superior edge of the patella; 2) five inches below the inferior edge of the patella; and 3) one inch above the peak of the medial malleolus. The presence of tenderness was elicited by manual compression of the calf and by palpation along the course of the femoral vein in the thigh. Elicitation for Homans' Sign was made.

The ultrasound examination was conducted with portable 5 megaHertz Doppler ultrasound velocity detectors.* We have previously described this procedure in detail.[26] In examination for occlusion, the ultrasound transducer was placed over the femoral vein at the inguinal ligament and the presence and quality of the spontaneous flow signal noted. The femoral spontaneous ultrasound signals are normally in phase with respiration. These signals may be abnormal with venous occlusion. Diminished or absent signals may be found at a site of occlusion and continuous high-pitched signals may be detected below a venous occlusion. However, we have noted that the augmented flow signal is a much more reliable indicator of occlusion than is the spontaneous flow signal, and our ultrasound examination has been based on the augmented flow signals. The augmented flow signal is a pulse wave induced by compression which is detectable by an ultrasound transducer. With the transducer in place over the femoral vein, the lower thigh is compressed manually and the presence of an augmented flow signal (A sound) noted. This is repeated with calf compression and passive foot dorsiflexion. If the vein is patent, the pulse wave will propagate toward the heart and be detected at the inguinal ligament. If the vein is occluded, the pulse wave is damped and there is either diminution or absence of the augmented flow signal.

Ultrasound examination was also employed to detect the presence of incompetent valves in the deep veins of the lower extremity. Induced augmented flow signals were used to determine if blood flow could move away from the heart. This would occur in the presence of nonfunctioning valves and indicates venous valve incompetency.

Throughout this study, we adhered to the following definitions of clinical and ultrasound abnormalities.

Clinical occlusion was defined as the presence of swelling or tenderness. Swelling was either pitting edema and/or a circumference difference of two centimeters or more at any of the three measured sites provided that neither extremity showed obvious muscular or osseous deformity. If a deformity were noted, circumferential measurement of swelling was not used and reliance was placed on pitting edema only.

Doppler ultrasound occlusion was defined as the absence or marked diminution of an augmented flow signal at the femoral vein following thigh or calf compression.

Second Examination

One week after operation, all patients in hospital were revisited by a nurse or technician. Women undergoing dilatation and curettage were re-examined on the second post-operative day. The clinical and Doppler ultrasound examinations for venous occlusion were repeated.

Third Examination

Two weeks after operation, all patients still in hospital were revisited again, and the clinical and ultrasound examinations were repeated.

Patients who had previously been studied and who returned for a second operation at the time of a subsequent hospitalization were not readmitted to the study.

The selection of risk factors associated with deep venous thrombosis in this study was based on two considerations. First, we reviewed conditions regarded as predisposing or at least as being associated with the occurrence of deep venous thrombosis. These potential risk factors were gathered on the basis of commonly held views in clinical practice and reports in the literature. Second, we restricted our selection because of resource limitations. This largely precluded us from examining risk factors which required laboratory testing because of the relatively large number of patients in the study. We have included clinical and ultrasound occlusion and pulmonary embolism as the risk factors. This was done to demonstrate how their occurrence was associated with coexistent and later developing clinical and ultrasound occlusion. The conditions examined as risk factors are listed below.

Pre-Operative Factors

1. Body build (weight to height relationship)
2. Age
3. Sex
4. Race
5. Type of operation planned
6. Hemoglobin
7. Previous venous thrombosis
8. Trauma (within one month)
9. Operations (within one month)
10. Pre-operative radiation
11. Pregnancy history

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* Smith Kline Instruments, 3400 Hillview Avenue, Palo Alto, California.

12. Smoking
13. Diabetes
14. Hypertension
15. Increased intra-abdominal pressure (organomegaly and/or acites)
16. Ovulatory suppressive treatment for contraception
17. Congestive heart failure
18. Activity
19. Extremity status (normal or abnormal extremity in terms of soft tissue and/or osseous deformity)
20. Previous pulmonary embolism
21. Symmetrical circumference differences of lower extremities
22. Pitting edema of lower extremities
23. Hyperpigmentation of lower extremities
24. Ulcer of lower extremities
25. Superficial varicosities of lower extremities
26. Tenderness of lower extremities
27. Homans' sign
28. Femoral spontaneous ultrasound signals
29. Clinical diagnosis of occlusion
30. Post-phlebitic syndrome (clinical diagnosis of venous valve incompetence)
31. Ultrasound diagnosis of occlusion
32. Ultrasound diagnosis of venous valve incompetence

Intra-Operative Factors

33. Type of operation performed
34. Type of anesthesia
35. Duration of operation
36. Patient position on operating room table
37. Amount of blood transfusions in operating room
38. Amount of intravenous fluids in operating room
39. Blood pressure
40. Presence of malignancy and status of control
41. Type of malignancy

General Post-Operative Factors

42. Day of initial ambulation
43. Second operation performed in post-operative period
44. Extension of hospital stay due to complications

Factors During First Post-Operative Week

45. Activity within 24 hours of examination
46. Change in extremity status
47. Temperature
48. Respiratory rate
49. Pulse rate
50. Development of pulmonary embolism
51. Non-embolic pulmonary complications
52. Operative site infection
53. Post-operative transfusions
54. Post-operative leg compression
55. Presence of congestive heart failure
56. Symmetrical circumference differences of lower extremities
57. Sequential circumference differences of lower extremities compared to previous examination
58. Pitting edema of lower extremities
59. Tenderness of lower extremities
60. Homans' sign
61. Femoral spontaneous ultrasound signals

Factors During Second Post-Operative Week

62. Temperature
63. Respiratory rate
64. Pulse rate
65. Development of pulmonary embolism
66. Non-embolic pulmonary complications
67. Operative site infection
68. Post-operative transfusions
69. Post-operative leg compression
70. Congestive heart failure
71. Symmetrical circumference differences of lower extremities
72. Sequential circumference differences of lower extremities compared to previous examination
73. Pitting edema of lower extremities
74. Tenderness of lower extremities
75. Homans' sign
76. Femoral spontaneous ultrasound signals

All data was recorded on code sheets, transferred to punch cards and stored on a magnetic disk for computer tabulation and analysis. The prevalence and incidence of clinical and ultrasound occlusion was determined for the entire patient population and further subdivided according to the type of operation performed.

Prevalence is defined as the number of instances of disease existing at a given point in time divided by the number of patients under consideration at that time. In this study, the time for determining prevalence was the pre-operative examination. Thus, prevalence indicates the extent of already existing venous occlusion in patients coming to operation. Incidence is defined as the number of new instances of disease found to occur in a specified time period, divided by the number of patients at risk during that time period. In this study, the time period was the first and second week post-operatively. In this report, prevalence and incidence of venous occlusion is presented as a percentage, while incidence of pulmonary embolism is provided in terms of instances per 1000 patients.

Single and multivariate analysis of risk factors[9] and their statistical significance was performed for several conditions in respect to pulmonary embolism and for the 76 potential risk factors listed above in regard to clinical and ultrasound occlusion. Single variate analysis provides information for a given single condition without regard to other factors. Multivariate analysis permits a quantitative comparison and corrects for the effects produced by dependency between factors. The reason for performing both single and multivariate analyses was that the computer program for multivariate analysis could only deal with up to ten factors at a time. Thus, we performed the single variate analysis first on the 76 risk factors for venous occlusion and subsequently used the most promising predictors in the multivariate analysis. Both the single and multivariate analyses provide data in the form of relative risk. Relative risk of a given factor is defined as a quantitative coefficient of how the presence of the factor is associated with an increased occurrence of an outcome (i.e. pulmonary embolism or venous thrombosis).* For example, if the relative risk coefficient of a factor in regard to a certain outcome is 2, then the presence of this factor indicates that the outcome is twice as likely to occur as when the factor is not present. Additional information with regard to risk is provided by determining the statistical significance of each relative risk coefficient. The statistical significance of each relative risk coefficient is derived on the basis of the magnitude of the coefficient and on the number of patients involved in calculating a particular relative risk coefficient.

Results

Only adult patients were admitted to the study and the average age of 2877 patients was 49.0 years. Distribution of patients by sex and race was as follows: 57.9% were male and 42.1% were female; 52.2% were white and 47.5% were black.

Pre-Operative Prevalence and Post-Operative Incidence

Pre-operative prevalence of clinical and ultrasound occlusion according to later length of stay in hospital is shown in Table 1. The prevalence is expressed in terms of clinical occlusion and ultrasound occlusion. The prevalence of occlusion in terms of positive clinical and ultrasound diagnoses was 8.7 and 1.3 percent respectively.

TABLE 1. *Pre-operative Prevalence of Clinical and Ultrasound Occlusion in Surgical Patients According to Length of Stay*

Definition	Number of Patients	Diagnosis of Occlusion Pre-Operatively by Method: Clinical	Ultrasound
Females undergoing D & C examined pre-operatively but who are not in hospital at 2 days post-operatively	145	1.4%	0.0%
Females undergoing D & C examined pre-operatively and on second post-operative day	43	4.7%	0.0%
Patients examined pre-operatively but who are not in hospital at seven days post-operatively	1077	6.7%	0.5%
Patients examined pre-operatively and seven days post-operatively	850	8.3%	1.3%
Patients examined pre-operatively, 7 days and 14 days post-operatively	762	13.7%	2.9%
Total	2877	8.7%	1.3%

All patients still in the hospital were re-examined one week and again two weeks after operation. Thus, of the 2877 patients to enter the study, 1655 patients underwent a second examination at one week after operation* and 762 patients underwent a third examination two weeks after operation. Tables 2 and 3 present the post-operative occurrence of clinical and ultrasound occlusion in the post-operative period. These results are shown as incidence of newly occurring occlusion, the persistence of positive findings, and the total occurrence of occlusion at one week and for the first and second weeks post-operatively. The number of patients available for determination of incidence was reduced not only by the number not in hospital at the time of the subsequent examination, but also by those already found to be positive for the particular evaluation under consideration at the initial examination. Since the prevalence of thrombosis by clinical examination was higher than by ultrasound examination, there were fewer patients to be considered in the incidence data in Table 2 compared to Table 3. Total occurrence of occlusion for a given time period is defined as all new cases of occlusion (incidence) plus persisting instances of occlusion from the pre-operative period. To simplify the presentation of results in patients examined twice during the post-operative period, reported positive diagnoses indicate that clinical or ultrasound occlusion was found at either or both post-operative examinations.

Table 2 shows the occurrence of venous occlusion diagnosed by clinical examination at one week and

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* The algebraic definition of relative risk is as follows: Let the notations below represent the terms to be considered,

	Number of patients: Outcome present	Outcome absent
Factor present	N(1, 1)	N(1, 0)
Factor absent	N(0, 1)	N(0, 0)

then,

$$\text{Relative Risk} = \frac{N(1,\ 1) \times N(0,\ 0)}{N(0,\ 1) \times N(1,\ 0)}$$

* Including 45 female patients who had dilatation and curettage and were re-examined on the second post-operative day.

TABLE 2. *Post-Operative Clinical Occlusion*

	First Week		First & Second Weeks		
Clinical Occlusion Pre-Operatively	Number of Patients	Clinical Occlusion Post-Operatively	Number of Patients	Clinical Occlusion Post-Operatively	Remarks
Absent	1478	7.3%	658	16.8%	Incidence of clinical occlusion in the post-operative period
Present	177	46.9%	104	65.4%	Presistence of pre-operative clinical occlusion into the post-operative period
Total	1655	11.5%	762	23.5%	Total occurrence of post-operative clinical occlusion = post-operative incidence + persisting pre-operative occlusion

during the first and second weeks post-operatively. The total occurrence of clinical occlusion at one week was 11.5%. The incidence of newly discovered clinical occlusion was 7.3% at the one-week post-operative examination. Persistence of clinical occlusion to the end of the first post-operative week was seen in 46.9% of the patients diagnosed pre-operatively as being occluded. The total occurrence of clinical occlusion during the first and second weeks in patients remaining in the hospital was 23.5%. The incidence of clinical occlusion for this period was 16.8%. A persistence of signs of clinical occlusion during the pre-operative examination was observed in 65.4% of the patients with an initial positive diagnosis.

Table 3 shows the occurrence of venous occlusion diagnosed by ultrasound examination in the post-operative period. As in Table 2, data is presented for the first week and the first and second weeks after operation. At one week, the total occurrence of ultrasound occlusion was 2.5%. The incidence rate of newly diagnosed ultrasound occlusions was 1.9%. Signs of ultrasound occlusions persisted in 33.3% of patients found to be occluded on the pre-operative examination. For the first and second weeks post-operatively, the total occurrence of ultrasound occlusion was 5.5%. The incidence for this period was 4.7%. Ultrasound occlusion persisted in 32.8% of patients found pre-operatively to be occluded.

Both Tables 2 and 3 show that persistence of clinical and ultrasound occlusion extending from the pre-operative to the post-operative period was relatively high. In order to demonstrate the extent to which persisting occlusion made up all occlusions in the post-operative period, the occurrence of new and persisting occlusion is presented in Tables 4 and 5.

Table 4 shows the breakdown of newly occurring and persisting clinical occlusion seen in the post-operative period. There were 191 patients with clinical occlusion at one week post-operatively. In 43.5% of these patients, clinical occlusion was a continuation of pre-operative findings. In patients staying in hospital at least two weeks post-operatively and examined at the end of the first and second weeks, there were 179 patients with clinical occlusion. In 38.0% of these patients, clinical occlusion was diagnosed pre-operatively.

Table 5 shows the distribution of newly diagnosed and persisting ultrasound occlusion in the post-operative period. Of 41 patients with an ultrasound diagnosis of occlusion at the end of the first post-operative week, 26.8% had persistence of pre-operative findings of ultrasound occlusion. In patients remaining in the hospital for at least two weeks after operation, there were 42 patients with ultrasound occlusion. In this group, 16.7% had ultrasound occlusion pre-operatively.

Figures 1 and 2 show the pre-operative prevalence and post-operative incidence of venous thrombosis in terms of diagnosis made by clinical means and ultrasound means respectively according to the type of opera-

TABLE 3. *Post-Operative Ultrasound Occlusion*

	First Week		First & Second Weeks		
Ultrasound Occlusion Pre-Operatively	Number of Patients	Ultrasound Occlusion Post-Operatively	Number of Patients	Ultrasound Occlusion Post-Operatively	Remarks
Absent	1622	1.9%	740	4.7%	Incidence of ultrasound occlusion in the post-operative period
Present	33	33.3%	22	32.8%	Persistence of pre-operative ultrasound occlusion into the post-operative period
Total	1655	2.5%	762	5.5%	Total occurrence of post-operative ultrasound occlusion = post-operative incidence + persisting pre-operative occlusion

TABLE 4. *Newly Occurring and Persisting Clinical Occlusion in the Post-Operative Period*

Patients with Post-Operative Occlusion In Whom Pre-Operative Clinical Occlusion Was:	First Week Number of Patients with Clinical Occlusion	Distribution	First & Second Weeks Number of Patients with Clinical Occlusion	Distribution	Remarks
Absent	108	56.5%	111	62.0%	Post-operative clinical occlusion which developed after the pre-operative examination
Present	83	43.5%	68	38.0%	Post-operative clinical occlusion which was present pre-operatively and persisted into the post-operative period
Total	191	100.0%	179	100.0%	

tive procedure performed. Lower extremity operations are subdivided into four types: arterial reconstruction, vein procedures, hip operations, and a general lower limb category which includes all lower extremity procedures except for arterial, vein or hip operations. Arterial reconstruction included aortic, iliac, femoral and popliteal bypass procedures or endarterectomies performed for arteriosclerotic occlusive disease. Venous procedures included vena cava ligations and partitions for thromboemboli, but most of the venous procedures were for the eradication of superficial varicosities. Hip operations included both hip joint replacements and operative fixation of fractures. General lower limb operations include soft tissue and osseous procedures of the thigh, leg or foot.

Figure 1 shows pre-operative prevalence and post-operative incidence in terms of a diagnosis of clinical occlusion of the deep venous system. All four categories of lower limb operations had a higher prevalence and incidence than the average values for the entire patient sample. Patients undergoing arterial reconstruction operations had the highest prevalence and incidence of clinical occlusion among the lower limb surgery group.

Figure 2 displays the prevalence and incidence results according to the diagnosis of venous occlusion made by ultrasound detection. Except for patients undergoing hip surgery seen pre-operatively and during the two week post-operative period, all categories of lower limb operations showed a higher prevalence and incidence of ultrasound occlusion than the average for the entire population sample. Hip surgery patients at one week post-operatively also showed a higher than average incidence of ultrasound occlusion. As with the clinical diagnosis, the prevalence and incidence of ultrasound occlusion was highest for patients undergoing lower limb arterial reconstruction operations.

Pulmonary Embolism

The incidence of pulmonary embolism during the first week post-operatively was 7.8 per 1000 patients. In this study, we define pulmonary embolism as a diagnosis made by the physician treating the patient based on historical, physical, electrocardiographic, radiologic or isotope scanning. The diagnosis of pulmonary embolism was made independently in all instances by the treatment physicians rather than the physicians involved in the study. The rate of pulmonary embolism was higher for patients undergoing lower limb operations (10.1 per 1000) compared to patients undergoing non-lower extremity operations (7.4 per 1000). Table 6 summarizes information regarding pulmonary embolism in the first week after operation. In Table 6, the incidence rate of pulmonary embolism is shown in respect to the presence of a diagnosis of venous occlusion made by either clinical or ultrasound examination and according to the type of operation performed. The incidence rate of pulmonary embolism in patients with no occlusion, clinical occlusion only, ultrasound occlusion only, and both clinical and ultrasound occlusion was 5.2, 11.8, 31.3 and 64.5

TABLE 5. *Newly Occurring and Presisting Ultrasound Occulsion in the Post-Operative Period*

Patients with Post-Operative Occlusion In Whom Pre-Operative Ultrasound Occlusion Was:	First Week Number of Patients with Ultrasound Occlusion	Distribution	First & Second Weeks Number of Patients with Ultrasound Occlusion	Distribution	Remarks
Absent	30	73.2%	35	83.3%	Post-operative ultrasound occlusion which developed after the pre-operative examination
Present	11	26.8%	7	16.7%	Post-operative ultrasound occlusion which was present pre-operatively and persisted into the post-operative period
Total	41	100.0%	42	100.0%	

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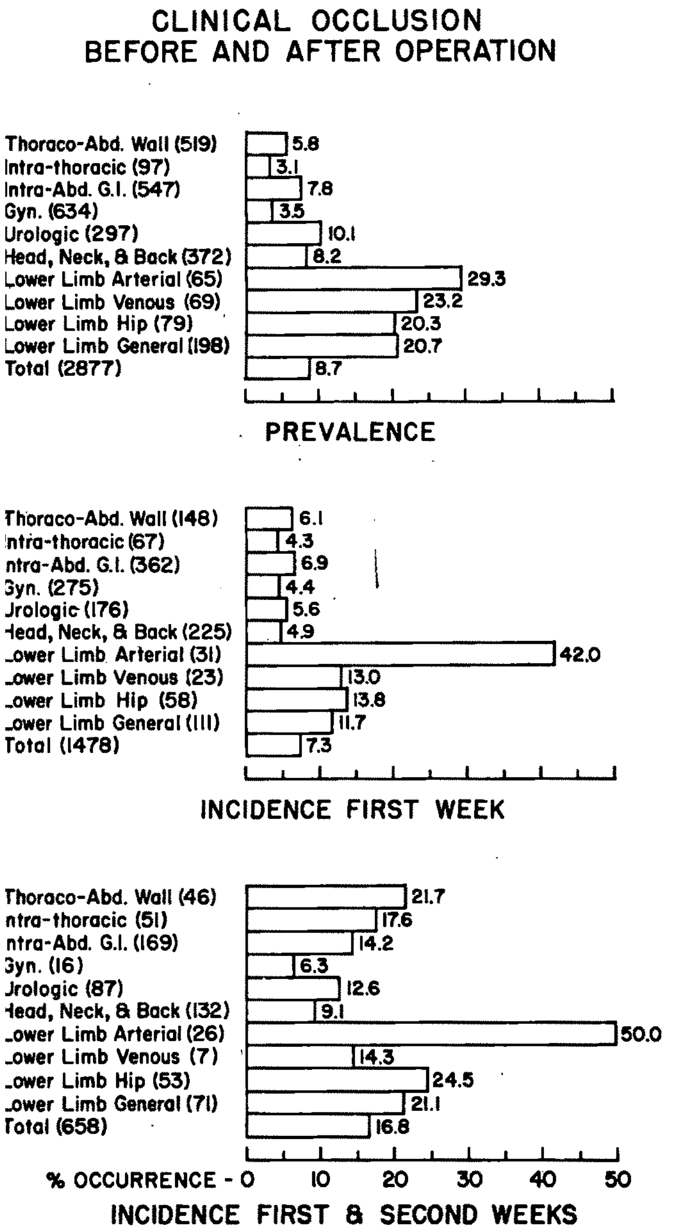

Fig. 1. Pre-operative prevalence and post-operative incidence of clinical occlusion according to type of operation performed. The numbers in parentheses alongside each operation designation represent the number of patients considered. Percentage figures are shown to the right of the bars.

per 1000 patients respectively. Within each of the four diagnostic categories, the number of pulmonary emboli were relatively few. However, there seemed to be little difference within each of the categories in respect to the type of operation performed. To test the point that the outcome of pulmonary embolism was related to the diagnosis of venous occlusion rather than the type of operation performed, a multivariate analysis was performed considering the occlusion diagnoses and the type of operation performed as risk factors for pulmonary embolism. The multivariate analysis revealed that the occurrence of post-operative pulmonary embolism was related to a diagnosis of clinical and ultrasound occlusion rather than the type of operation performed. This confirmed our interpretation of the incidence rate data in Table 6 that the higher incidence of pulmonary embolism in the patients who underwent lower limb operation was attributable primarily to the higher occurrence of clinical and ultrasound occlusion in this group. In

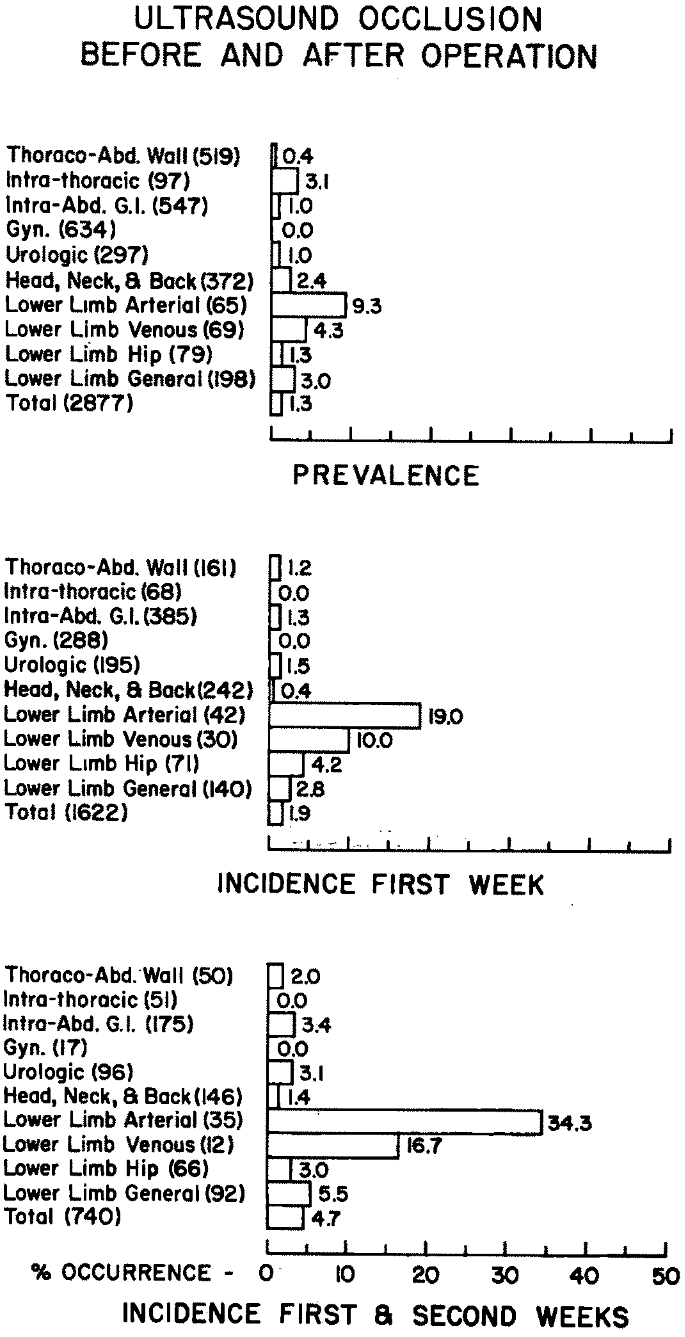

Fig. 2. Pre-operative prevalence and post-operative incidence of ultrasound occlusion according to type of operation performed. The numbers in parentheses alongside each operation designation represent the number of patients considered. Percentage figures are shown to the right of the bars.

TABLE 6. *Incidence of Pulmonary Embolism in the First Post-Operative Week*

Diagnosis of Occlusion Made Pre-Operatively and/or One Week Post-Operatively by Method								
Clinical	Ultrasound	Type of Patients	Patients with Pulmonary Embolism		Number of Patients		Rate P.E. per 1000 Patients	
No	No	Patients with non-lower limb operations	6		1167		5.1	
		Patients with limb operations	1		171		5.8	
		Subtotal		7		1338		5.2
Yes	No	Patients with non-lower limb operations	2		160		12.5	
		Patients with limb operations	1		94		10.6	
		Subtotal		3		254		11.8
No	Yes	Patients with non-lower limb operations	1		17		58.0	
		Patients with limb operations	0		15		0.0	
		Subtotal		1		32		31.3
Yes	Yes	Patients with non-lower limb operations	1		13		76.9	
		Patients with limb operations	1		18		55.5	
		Subtotal		2		31		64.5
		Total		13		1655		7.8

this multivariate analysis, the relative risk coefficients for clinical and ultrasound occlusion in respect to the development of pulmonary embolism were 2.4 and 6.4 respectively. This means that the presence of clinical occlusion was associated with a 2.4 times increased incidence of pulmonary embolism while the presence of ultrasound occlusion was associated with a 6.4 times increased incidence of pulmonary embolism compared to the occurrence of pulmonary embolism in patients without clinical or ultrasound occlusion.

Thirty-seven patients died during the two-week post-operative period of observation and autopsies were performed in 20 of the deaths. Death was attributed to pulmonary embolism in two patients, neither of whom underwent postmortem examination. In one of these two deaths, neither clinical or ultrasound occlusion was detected during life. In the other, a diagnosis of both clinical and ultrasound occlusion was made prior to death.

Relative Risk Analysis of Factors Associated with Venous Occlusion

A single variate analysis of relative risk and its significance was performed for each of the pre-operative conditions presented under Methodology (above) as potential risk factors for clinical or ultrasound occlusion in terms of pre-operative prevalence and incidence at the end of the first post-operative week. There were too few cases at two weeks post-operatively to permit a meaningful determination of statistical significance at this time interval. Intra-operative and post-operative factors were not evaluated in terms of prevalence but were analyzed in terms of incidence of venous occlusion one week post-operatively. On the single variate analysis, 11 of 76 risk factors were significant. All were pre-operative except for the type of operation performed. These factors were employed in the multivariate analyses and were as follows:

(1) Type of operation
(2) Older age (considered by decades)
(3) Congestive heart failure (pre-operative)
(4) Abnormal lower extremity (pre-operative). Definition: soft tissue and/or osseous deformity
(5) Inactivity (pre-operative). Definition: limited (bathroom privileges only) and complete bed rest
(6) Post-phlebitic syndrome
(7) Ultrasound occlusion (pre-operative)
(8) Ultrasound diagnosis of incompetent lower extremity deep valves (pre-operative)
(9) Previous pulmonary embolism (pre-operative)
(10) Abnormal femoral spontaneous ultrasound signal (pre-operative)
(11) Clinical occlusion (pre-operative)

The multivariate risk factor analysis revealed that the most important risk factor by at least a tenfold margin was the type of operation performed. The relative risk coefficient was very highly significant ($p < 0.001$). The operations with the greater propensity for venous occlusion were those on the lower limb. Within the limb operation group, arterial reconstruction presented the highest risk. The effect of lower limb operations was so strong in the multivariate analysis that the existence of lesser but still potentially significant risk factors was obscured when type of operation was used in the analysis. Since the patients undergoing lower extremity operations were so distinctly at greater risk for a diagnosis of venous occlusion than patients having other types of operations and since patients undergoing non-lower extremity operations were not at risk for this factor, we separated patient data according to the two types of operation. We performed another multivariate risk factor analysis using data separated according to patients undergoing non-lower extremity operations and patients undergoing lower extremity operations. Tables 7 and 8 show the results of the multivariate risk factor analysis performed on data from the two patient population samples. The relative risk coefficient and its level of significance is shown for each factor. The highest relative risk coefficients were not necessarily those of greatest significance. Statistical significance was determined by the magnitude of the relative risk and the number of patients represented. If the number of patients for consideration of a particular risk factor were low, statistical significance may not have been reached even though the relative risk were high.

Table 7 summarizes relative risk factor information with respect to prevalence of clinical and ultrasound occlusion. For patients undergoing non-lower extremity operations, the significant risk factors associated with already existing clinical occlusion were older age, presence of abnormal extremities, inactivity, and the presence of the post-phlebitic syndrome. In these same patients, the significant risk factors associated with pre-operative ultrasound occlusion were inactivity, ultrasound diagnosis of deep vein incompetence, history of previous pulmonary embolism, and abnormal femoral spontaneous ultrasound signals. Inactivity was the only risk factor in the non-lower extremity operation patients to be significant for both clinical and ultrasound occlusion.

Table 7 also displays the relative risk factors associated with the prevalence of venous occlusion in patients undergoing lower extremity operations. In terms of pre-operative clinical occlusion, the post-phlebitic syndrome was the only significant risk factor. In terms of pre-operative ultrasound occlusion, the significant risk factors were inactivity, the post-phlebitic syndrome, and abnormal femoral spontaneous ultrasound signals. The presence of the post-phlebitic syndrome was a common significant risk factor for the diagnosis made both by clinical and ultrasound means in patients undergoing lower limb operations.

Table 8 shows relative risk factor data in respect to the incidence of clinical and ultrasound occlusion discovered one week after operation. The ten risk factors are the same as in Table 7. For patients who underwent non-lower extremity operations, the significant risk factors for the post-operative occurrence of clinical occlusion are inactivity, history of previous pulmonary embolism, and abnormal femoral spontaneous ultrasound signals. In these patients, the only significant risk factor associated with the development of ultrasound occlusion one week post-operatively was inactivity. This factor was common as a significant predictor of both clinical and ultrasound diagnoses in this group of patients.

Table 8 also summarizes relative risk factors for the one week incidence of venous occlusion for patients who had undergone lower limb operations. No significant factors emerged from the battery of ten in respect to clinical occlusion. Although pre-operative ultrasound occlusion showed a high relative risk coefficient (10.68), the number of instances for this occurrence were too small to reach statistically significant levels. Two factors emerged as significant in association with post-operative ultrasound occlusion. These were abnormal extremities and the presence of deep venous valve incompetence on the pre-operative ultrasound examination.

We summarize the relative risk factor analysis in the following manner.

For the patients undergoing non-lower extremity operations, the most consistent risk factor was pre-operative inactivity of the patient. This factor was significant for both the prevalence and incidence of clinical as well as ultrasound occlusion. Pre-operative inactivity was defined as either limited activity meaning bathroom privi-

TABLE 7. *Relative Risk Factors for the Prevalence of Venous Occlusion*

Variable	Non-Lower Limb Operations Clinical Occlusion	Non-Lower Limb Operations Ultrasound Occlusion	Lower Limb Operations Clinical Occlusion	Lower Limb Operations Ultrasound Occlusion
Age	1.16*	1.11	1.03	1.60
Congestive Heart Failure	1.40	0.59	0.56	0.09
Abnormal Extremity	2.20***	1.25	2.27	0.90
Inactivity	2.18***	2.27**	1.58	4.86*
Post-Phlebitic Syndrome	5.81***	0.68	3.53**	54.15*
Ultrasound Occlusion	1.30	—	0.56	—
Ultrasound Incompetent Valves	1.01	3.46**	1.09	2.39
Previous Pulmonary Embolism	0.85	6.36*	1.79	8.58
Abnormal Femoral Spontaneous Ultrasound Signal	0.73	10.49***	3.78	61.60**
Clinical Occlusion	—	1.03	—	0.33

Significant levels:
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

TABLE 8. *Relative Risk Factors for the Incidence of Venous Occlusion at One Week Post-Operatively*

	Non-Lower Limb Operations		Lower Limb Operations	
Variable	Clinical Occlusion	Ultrasound Occlusion	Clinical Occlusion	Ultrasound Occlusion
Age	1.09	1.36	1.38	0.79
Congestive Heart Failure	1.30	1.32	1.64	0.42
Abnormal Extremity	0.77	1.33	3.40	20.30***
Inactivity	1.55**	2.04**	0.40	0.73
Post-Phlebitic Syndrome	1.85	1.35	0.48	0.43
Ultrasound Occlusion	0.72	—	10.68	—
Ultrasound Incompetent Valves	0.98	1.13	1.23	6.32**
Previous Pulmonary Embolism	5.50**	0.02	3.43	4.36
Abnormal Femoral Spontaneous Ultrasound Signal	2.31**	0.51	1.39	0.46
Clinical Occlusion	—	1.72	—	0.91

Significance levels:
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

leges only or complete bed rest for 24 hours or longer prior to the initial examination. Single variate analysis showed that complete bed rest carried a higher risk for venous occlusion than limited activity. Thus, pre-operative inactivity was the dominant risk factor for venous occlusion and the degree of inactivity was important in determining the risk of venous occlusion. Several other risk factors were associated with either clinical or ultrasound occlusion at one or the other time of examination for occlusion in patients undergoing non-lower extremity surgery. However, none of these were as consistent as inactivity as a risk factor.

For patients undergoing lower limb operation, the most important risk factor was the lower limb operation. After that, a single factor did not dominate the analysis. The post-phlebitic syndrome seemed important in prevalence while abnormal extremities and ultrasound evidence of incompetent venous valves were significant in incidence. Although different, the significant secondary risk factors represented local abnormalities of the lower extremities (i.e. either soft tissue or osseous abnormality or suggestive evidence of previous venous disease). Thus, the most important risk factor for patients in hospital for lower limb surgery was the lower limb operation itself being performed for lower extremity disease. Of secondary but still significant importance, were associated abnormalities of the lower limb.

Discussion

This study was designed to consider specifically the prevalence and incidence of venous thrombosis, the relation of diagnosed venous thrombosis to pulmonary embolism, and the identity and importance of risk factors associated with venous thrombosis. The results achieve the basic objectives of the study. However, the results provide additional insights into the methodology, stress the importance in distinguishing between prevalence and incidence in surgical patients, and indicate that surgical patients epidemiologically probably should be distinguished according to whether they are undergoing lower extremity operations or other types of procedures.

A striking feature in the prevalence and incidence figures was the wide disparity between clinical and ultrasound diagnosis. The frequency of occurrence of clinical occlusion was up to ten times greater than ultrasound occlusion in the same patients examined at the same time by both methods. This raises questions in regard to methodology and the validity of employing clinical and ultrasound examination in studying the epidemiology of venous thrombosis.

These dissimilarities in results probably arise from differences in the accuracy as measured by the sensitivity and specificity of the two methods. In a previous study, we found that compared to venography, the ultrasound method was moderately sensitive and highly specific, while the clinical examination was neither very sensitive or specific.[27] We believe that the higher occurrence of occlusion detected clinically may be due to a large number of false positive clinical diagnoses. In other words, we believe that many of the instances of swelling or tenderness which we considered as venous occlusion clinically were in fact due to conditions other than venous thrombosis. The ultrasound method, on the other hand, tends to underdiagnose because it may miss small partially occluding thrombi, particularly in the presence of alternate or collateral channels. Complete occlusions of the femoral and popliteal veins are identified with a high degree of accuracy.[28] These differences in occurrence figures vary also with the published results obtained with other methods such as ^{125}I fibrinogen scanning[11,17] and electrical impedance.[29] Such dissimilarities may be due not only to differences in accuracy but also to differences in study methods and study populations.

The greatly varied results obtained with post-mortem studies, venography, isotope scanning and the non-invasive (ultrasound and electrical impedance) techniques indicates that we cannot yet clearly define pathogenically significant venous thrombosis. In the final analysis, this may be accomplished by relating diagnostic measures to the most relevant endpoint of deep venous thrombosis; namely, pulmonary embolism. On this basis, there is evidence from this study that both clinical and ultrasound methods have validity in the diagnosis of venous occlusion.

The results of the present study show that pulmonary embolism occurred more frequently in patients with clinical and ultrasound occlusion than in patients without signs of clinical or ultrasound occlusion. The total number of patients to develop pulmonary embolism in the first post-operative week was relatively small. Nevertheless, it is possible to conclude that clinical and ultrasound occlusion were definitely associated with a higher occurrence of diagnosed pulmonary embolism. This reflects upon the value of these procedures as diagnostic tools and as methods of measuring venous thrombosis in an epidemiologic study. While both methods showed value, the ultrasound method was two to three times superior to the clinical method on the basis of their respective relative risk coefficients. Both techniques no doubt have limitations as evidenced by the fact that most of the clinically diagnosed pulmonary emboli did not have clinical or ultrasound occlusion. Yet, even so, the simplicity and safety of the methodology provides a comparatively useful set of diagnostic tools for epidemiologic study in surgical patients. However, the limitations of clinical and ultrasound methods must be borne in mind and the results of each diagnostic examination for venous occlusion must be regarded in relative rather than absolute terms.

The occurrence of lower extremity deep venous occlusion in this study is presented according to pre-operative prevalence and post-operative incidence. We believe that it is important to make this distinction because it shows to what extent post-operative venous occlusion actually may have begun before operation. The results of this study revealed that about two-fifths of all clinical occlusions seen after operation were present pre-operatively and constituted a persistence of findings into the post-operative period. The proportion of post-operative ultrasound occlusion extending from the pre-operative examination was less but still over one-fourth of all positive ultrasound diagnoses at one week post-operatively. This difference between clinical and ultrasound persistence of findings may be due to differences in sensitivity and specificity. Nevertheless, it appears that a sizable proportion of post-operative venous occlusion was present pre-operatively. This indicates that the underlying disease and condition of the patient was an important determinant of pre-operative prevalence and, as these findings persisted, in the total occurrence of venous disease in the post-operative period. This is suggested by the data in Table 1 which shows that the pre-operative prevalence of both clinical and ultrasound occlusion was greater in patients who stayed in hospital longer after their operations. Studies with ^{125}I fibrinogen have indicated that venous thrombosis may commence during operation.[11] Our study suggests that, compared to post-operative incidence, there may be significant venous occlusion in patients prior to operation which continues and may partly account for the high incidence of pulmonary embolism observed by Coon and Coller in the first few days after operation.[7]

Patients undergoing lower extremity operations have such a higher prevalence and incidence of venous occlusion that they probably should be considered separately, for epidemiologic purposes, from patients undergoing non-lower limb operations. Multivariate analysis of risk factors confirmed this finding and indicated further that the distinguishing factor was indeed the type of operation performed and not associated factors in the battery of potential high risk factors tested.

The importance of the type of operation performed in regard to prevalence and incidence in patients has not been previously emphasized. It has been known that patients with lower extremity fractures are more prone to develop venous thrombosis, particularly after operation.[16,17,23–25] Our study stresses, however, that this is not restricted to traumatized extremities but occurs with all types of limb operations. The highest prevalence and incidence of deep venous occlusion was seen in patients undergoing arterial reconstruction for lower extremity arteriosclerotic occlusive disease. These results are at variance with older published results which indicate that laparotomy, particularly associated with extensive dissection and organ resection, was associated with the highest occurrence of venous thrombosis.[1]

By considering the non-lower limb operation patients separately from patients undergoing lower extremity surgery, it is possible to discern epidemiologic differences in the two patient population samples. In patients undergoing non-lower limb operation, the most consistent risk factor was patient inactivity prior to operation. In patients undergoing limb surgery, the primary factor was the surgery *per se* and the secondary factors were mainly abnormalities of the extremities. Thus, in patients undergoing operations other than on the lower extremity, the most important risk factor was a condition leading to venous stasis. In contrast, the most important risk factors for patients undergoing limb operations were local, relating primarily to operative trauma and the underlying diseases in the extremity.

The failure to identify certain conditions as significant risk factors requires further comment. First, it is possible that with a larger study population, risk factors which did not reach significant levels may have attained significance. Second, other factors if present in different stages may have exerted an influence. For example, carcinoma has been regarded as a predisposing factor to venous thrombosis, yet it was not significant in this study. This may be due to the fact that most operations for carcinoma in this study were performed relatively early in the course of the neoplastic disease and the patients were followed for only two weeks. On this basis, we cannot conclude that any of the potential risk factors considered in our analysis are unimportant. We can only identify the most important ones in respect to the type of study performed. Furthermore, there are many risk factors (e.g. hematologic tests) which we did not consider and which could possibly overshadow the factors which seem important in this analysis.

Conclusions and Summary

A prospective epidemiologic study of lower extremity deep venous thrombosis was conducted in patients undergoing elective operations on general and specialty surgery services. Clinical and Doppler ultrasound examinations were performed simultaneously to detect venous occlusion before and after operation. The purpose of the study was to determine the pre-operative prevalence and post-operative incidence of venous occlusion, the association of venous thrombosis with pulmonary embolism, and the identification of risk factors associated with the pre-operative prevalence and post-operative incidence of venous thrombosis. The major findings of the study conducted in 2877 patients were as follows:

1. The prevalence and incidence of venous occlusion was higher in terms of the clinical diagnosis than the ultrasound diagnosis. This was probably due to differences in accuracy of the two methods with ultrasound being the more precise measure of venous thrombosis.

2. Pre-operative prevalence by clinical and ultrasound examination was 8.7% and 1.3% respectively. Post-operative incidence of newly developed clinical and ultrasound occlusion was 7.3% and 1.9% respectively at one week after operation. For patients staying in the hospital for two weeks after operation, the incidence of clinical and ultrasound occlusion was 16.8% and 4.7% respectively.

3. There was a significant persistence of the findings of occlusion in patients found to have clinical and ultrasound venous occlusion pre-operatively. Patients with persistent signs of occlusion constituted a sizable proportion of all post-operative venous occlusions. Persistence of signs was greater in terms of clinical occlusion than ultrasound occlusion. Newly occurring occlusion plus persisting pre-operative occlusion constituted a total post-operative occurrence of 11.5% and 2.5% respectively for clinical and ultrasound occlusion at one week post-operatively. The total occurrence for the first and second weeks post-operatively was 23.5% and 5.5% respectively for clinical and ultrasound occlusion.

4. Prevalence and incidence of venous occlusion varied markedly according to the type of operation performed. Patients undergoing operations upon their lower extremities had a significantly higher prevalence and incidence of venous occlusion than patients undergoing non-lower limb operations. Patients undergoing arterial reconstruction operations for lower extremity arteriosclerotic occlusive disease had the highest occurrence of venous occlusion.

5. The incidence of post-operative pulmonary embolism was higher in patients undergoing lower extremity operations. However, this was due to the fact that there was a higher proportion of venous occlusion in patients with lower extremity operations.

6. The ultrasound diagnosis of venous occlusions was more closely associated with the post-operative incidence of pulmonary embolism than was the clinical diagnosis of venous occlusion.

7. Potential risk factors associated with venous occlusion were considered from historical, physical examination, and ultrasound examination information. The most important single factor was the type of operation performed with lower limb operations emerging as the greatest risk factor. This indicated that the higher prevalence and incidence for patients undergoing this type of procedure was due mainly to the operation rather than other associated factors which were analyzed.

8. The marked differences in prevalence and incidence in venous occlusion suggested that patients undergoing non-lower limb operations should be considered separately from patients undergoing lower limb surgery for purposes of epidemiologic evaluation. This revealed that for patients undergoing non-lower limb surgery, the most consistent risk factor in terms of clinical and ultrasound prevalence and incidence was pre-operative inactivity of the patient. On the other hand, the greatest risk factors for patients undergoing lower limb operation were local: first, the operation itself; and, second, other abnormalities associated with previous soft tissue, osseous or venous disease of the extremities.

9. This study indicated that pre-operative conditions were extremly important in determining the presence of venous thrombosis post-operatively. This interpretation was based on the high proportion of venous thrombosis post-operatively which was actually a continuation of pre-operative disease and the demonstration that pre-operative inactivity was the most significant risk factor associated with venous thrombosis in patients undergoing non-lower extremity operations.

Acknowledgment

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References

1. Barker, N. W., Nygaard, K. K., Walters, W. and Priestly, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. I. Incidence in Various Types of Operations. Proc. Mayo Clinic, **15**:769, 1940.
2. Barker, N. W., Nygaard, K. K., Walters, W. and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. II. Predisposing Factors. Proc. Mayo Clinic, **16**:1, 1941.
3. Barker, N. W., Nygaard, K.K., Walters, W. and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. III. Time of Occurrence During the Postoperative Period. Proc. Mayo Clinic, **16**:17, 1941.
4. Bruzelius, S.: Dicoumarin in Clinical Use: Studies on its Prophylactic and Therapeutic Value in the Treatment of Thromboembolism. Acta. Chir. Scand., **92**:Suppl. 100, 1945.
5. Byrne, J. J.: Phlebitis. A Study of 748 Cases at the Boston City Hospital. N. Engl. J. Med., **253**:579, 1955.
6. Coon, W. W., MacKenzie, J. W. and Hodgson, P. E.: A Critical Evaluation of Anticoagulant Therapy in Peripheral Venous Thrombosis and Pulmonary Embolism. Surg., Gynecol. Obstet., **106**:129, 1958.
7. Coon, W. W. and Coller, F. A.: Some Epidemiologic Considerations of Thromboembolism. Surg., Gynecol. Obstet., **109**:487, 1959.
8. DeBakey, M. E.: A Critical Evaluation of the Problem of Thromboembolism. Surg., Gynecol. & Obstet., **98**:1, 1954.
9. Dunn, J. P., Ipsen, J., Elsom, K. O. and Ohtani, M.: Risk Factors in Coronary Artery Disease, Hypertension and Diabetes. Amer. J. Med. Sci., **259**:309, 1970.
10. Flanc, C., Kakkar, V. V. and Clarke, M. B.: The Detection of Venous Thrombosis of the Legs Using ^{125}I-Labelled Fibrinogen. Brit. J. Surg., **55**:742, 1968.
11. Flanc, C., Kakkar, V. V. and Clarke, M. B.: Postoperative Deep Vein Thrombosis Effect of Intensive Prophylaxis. Lancet, **1**:477, 1969.
12. Fowler, E. F. and Bollinger, J. A.: Pulmonary Embolism: A Clinical Study of Ninety-Seven Fatal Cases. Surgery, **36**: 650, 1954.
13. Freiman, D. G., Suyemoto, J. and Wessler, S.: Frequency of Pulmonary Thromboembolism in Man. N. Engl. J. Med., **272**:1278, 1965.
14. Freiman, D. G.: Surgical Conditions as Risk Factors in the Development of Venous Thrombosis. *In* The Epidemiology of Venous Thrombosis. The Milbank Memorial Fund Quarterly, **50**:60, 1972.
15. Gibbs, N. M.: Venous Thrombosis of the Lower Limbs with Particular Reference to Bed Rest. Brit. J. Surg., **45**:209, 1957.
16. Harris, W. H., Salzman, E. W. and DeSanctis, R. W.: The Prevention of Thromboembolic Disease by Prophylactic Anticoagulation. J. Bone Surg., **49-A**:81, 1967.
17. Kakkar, V. V.: The ^{125}I-Labeled Fibrinogen Test and Phlebography in the Diagnosis of Deep Vein Thrombosis. *In* The Epidemiology of Venous Thrombosis. The Milbank Memorial Fund Quarterly **50**:206, 1972.
18. Lambie, J. M., Mahaffy, R. G., Barber, D. C., *et al.*: Diagnostic Accuracy in Venous Thrombosis. Brit. Med. J., **2**:142, 1970.
19. Mavor, G. E. and Galloway, J. M. D.: The Iliofemoral Venous Segment as a Source of Pulmonary Emboli. Lancet, **1**:871, 1967.
20. Miller, R. and Berry, J. B.: Pulmonary Infarction: A Frequently Missed Diagnosis. Am. J. Med. Sci., **222**:197, 1951.
21. Ochsner, A., DeBakey, M. E., DeCamp, P. T. and DaRocha, E.: Thrombo-Embolism: An Analysis of Cases at the Charity Hospital in New Orleans Over a 12-Year Period. Ann. Surg., **134**:405, 1951.
22. Paterson, J. C. and McLachlin, J.: Precipitating Factors in Venous Thrombosis. Surg., Gynecol. Obstet., **98**:96, 1954.
23. Pinto, D. J.: Controlled Trial of an Anticoagulant (Warfarin Sodium) in the Prevention of Venous Thrombosis Following Hip Surgery. Brit. J. Surg., **57**:349, 1970.
24. Saltzman, E. W., Harris, W. H. and DeSanctis, R. W.: Anticoagulation for Prevention of Thromboembolism Following Fractures of the Hip. N. Engl. J. Med., **275**:122, 1966.
25. Sevitt, S. and Gallagher, N.: Venous Thrombosis and Pulmonary Embolism: A Clinico-Pathological Study in Injured and Burned Patients. Brit. J. Surg., **48**:475, 1961.
26. Sigel, B., Popky, G. L., Wagner, D. K., *et al.*: A Doppler Ultrasound Method for Diagnosing Lower Extremity Venous Disease. Surg., Gynecol. Obstet., **127**:339, 1968.
27. Sigel, B., Popky, G. L., Mapp, E. M., *et al.*: Evaluation of Doppler Ultrasound Examination: Its Use in Diagnosis of Lower Extremity Venous Disease. Arch. Surg., **100**:535, 1970.
28. Sigel, B., Felix, Jr., W. R., Popky, G. L. and Ipsen, J.: Diagnosis of Lower Limb Venous Thrombosis by Doppler Ultrasound Technique. Arch Surg., **104**:174, 1972.
29. Wheeler, H. B., Mullick, S. C., Anderson, J. N. and Pearson, D.: Diagnosis of Occult Deep Vein Thrombosis by a Non-Invasive Technique. Surgery, **70**:20, 1971.

Keflin® I.V.
sodium cephalothin
2 Gm.* in 100-ml. ampoule

10 years of clinical experience

Keflin was made available for clinical investigation early in 1962 and was marketed on September 4, 1964.

Since the introduction of Keflin, the susceptibilities of commonly encountered organisms, as measured by in-vitro methods, have not changed significantly. See brief summary for indications.

Lilly

*equivalent to cephalothin

Please turn page for summary of prescribing information.

Brief Summary.
Consult the package literature for prescribing information.

Actions: Keflin® (sodium cephalothin, Lilly) is a broad-spectrum antibiotic. Following a single 1-Gm. intravenous dose, blood levels have been about 30 mcg. per ml. at fifteen minutes. Dosages of 2 Gm. given intravenously over a thirty-minute period have produced serum concentrations of 80 to 100 mcg. per ml. one-half hour after the infusion.

The antibiotic passes readily into body fluids, e.g., pleural, joint, bile, and ascitic fluids.

Indications: Keflin is indicated for the treatment of serious infections caused by susceptible strains of the designated micro-organisms in the diseases listed below.

Respiratory tract infections caused by *Diplococcus pneumoniae*, staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Klebsiella*, and *Hemophilus influenzae*

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Genito-urinary tract infections caused by *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*

Septicemia, including endocarditis, caused by *D. pneumoniae*, staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Streptococcus viridans*, *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*

Gastro-intestinal infections caused by *Salmonella* and *Shigella* species

Meningitis caused by *D. pneumoniae*, group A beta-hemolytic streptococci, and staphylococci (penicillinase and nonpenicillinase-producing)

Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [071873]

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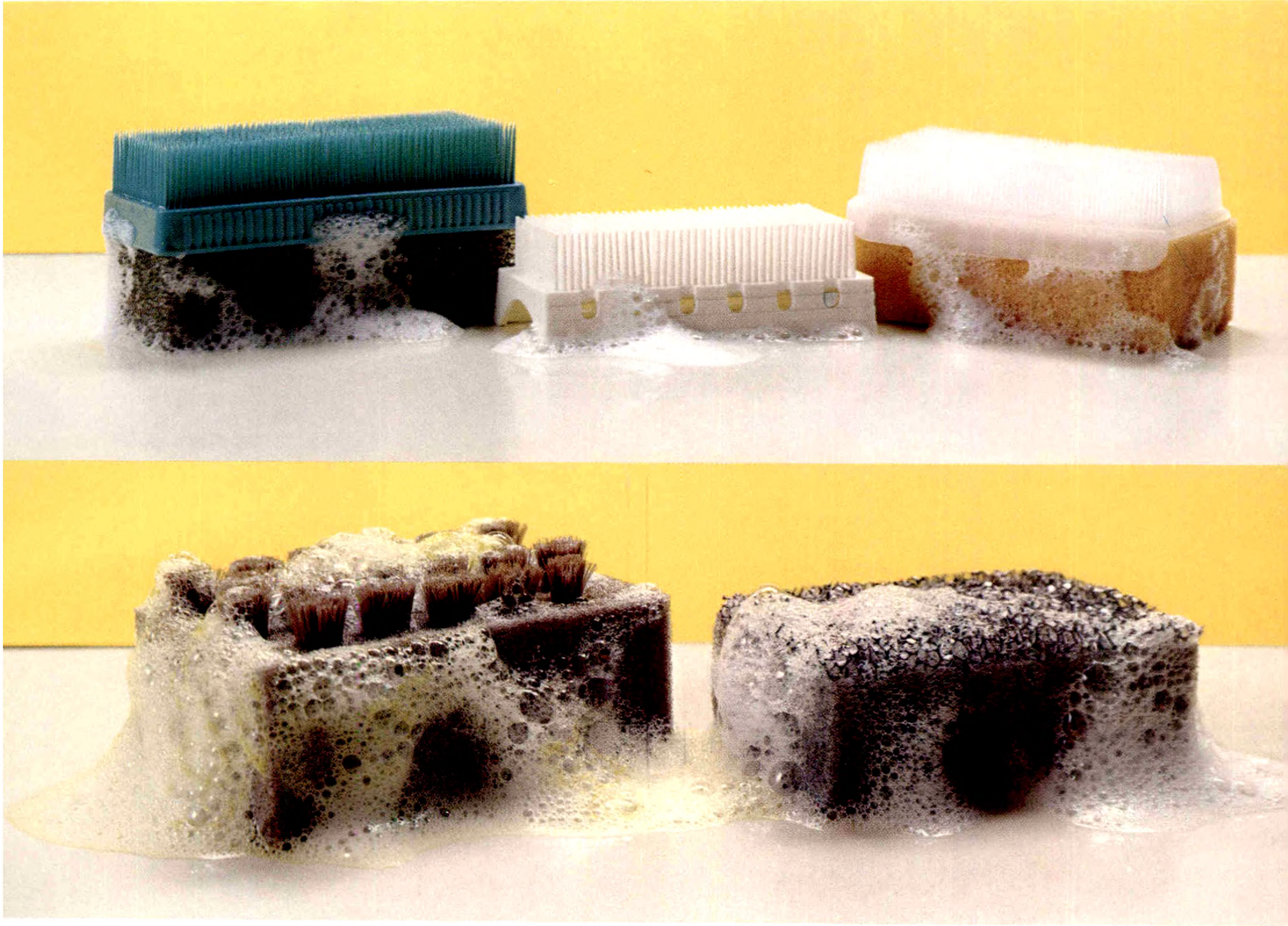

But PRE·OP® products can: More suds. Better cleaning. More flexible brushes. Greater variety. Sterile packaging.

Sure, some of the other scrub products give you some of these benefits. But only PRE·OP products give you all of them. Choose either PRE·OP* Surgical Scrub Sponges or PRE·OP *plus*—the versatile sponge-brush combination that can be as firm or as soft as you wish. They're single-use products, so there's no cross-contamination. And they're economical, too. Available with either iodophor or hexachlorophene.

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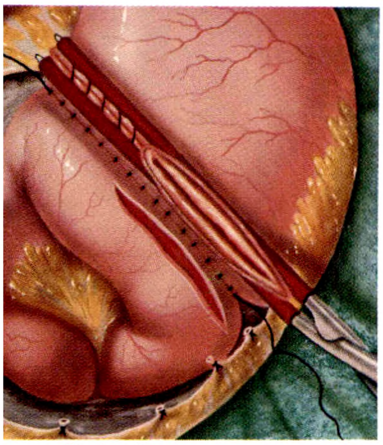
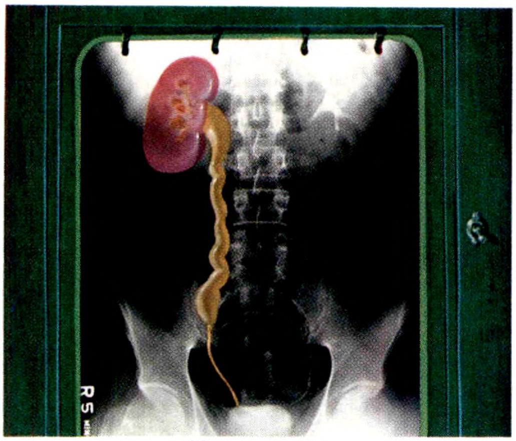
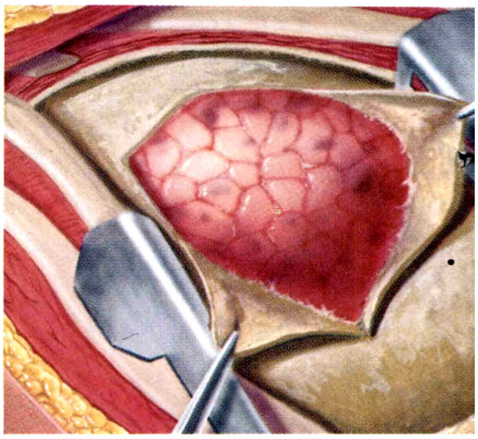
PRE·OP Sponges and PRE·OP *plus* with hexachlorophene are bacteriostatic skin cleansers for surgical scrubbing use only. Hands should be rinsed thoroughly after use. They are impregnated with an anhydrous soap concentrate containing the aqueous solution equivalent of 3% w/w hexachlorophene. It is not intended for use on burned or denuded skin, for routine prophylactic total body bathing, or for general patient care.

severe pain associated with many everyday hospital situations.

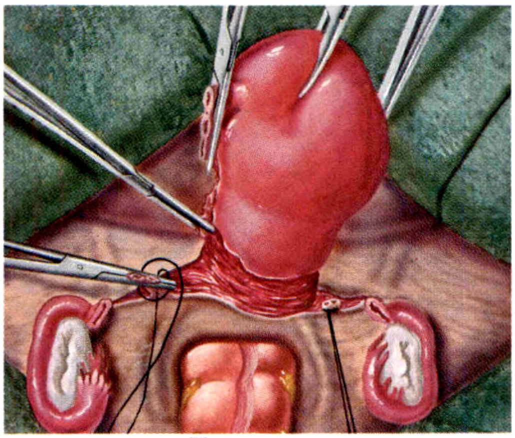

Gastrectomy

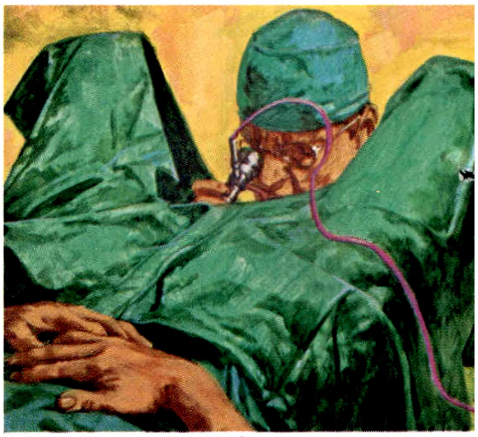


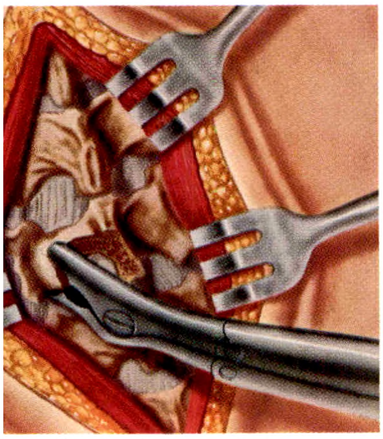
Ureteral colic

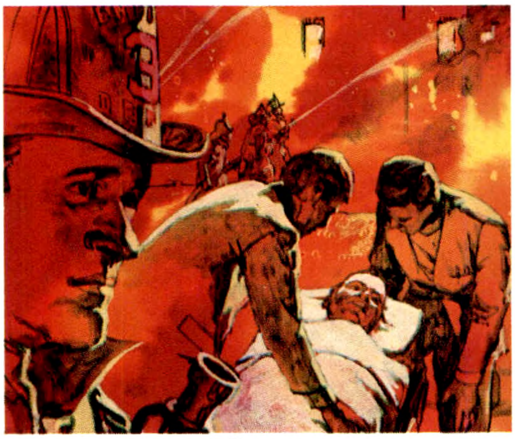

Thoracic surgery

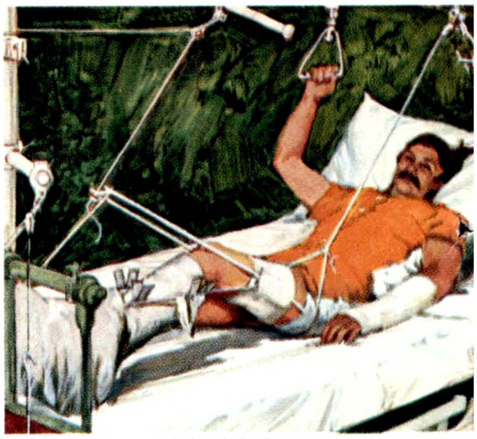
Traumatic pain


Hysterectomy

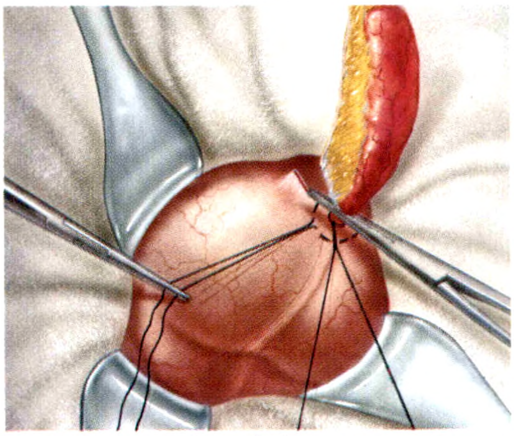

Endoscopy

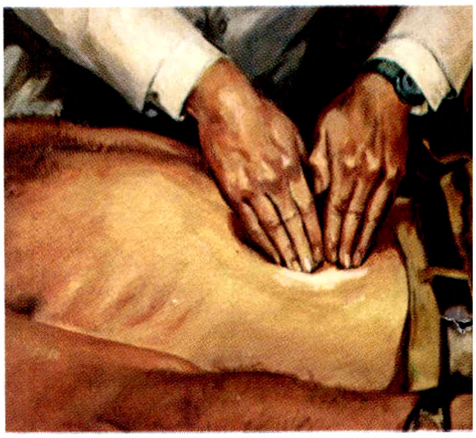

Laminectomy


Burns


Multiple fractures

Acute bursitis


Appendectomy


Intestinal colic

Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. See full instructions and warnings on last page.

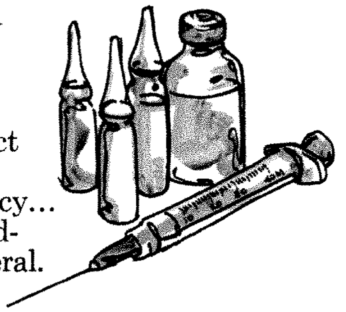
the unextreme injectable for serious pain

Talwin doesn't go to extremes.

Yet, Talwin relieves serious pain (moderate to severe pain) in the great majority of everyday hospital situations.

For most serious pain—Talwin has in fact been shown comparable to narcotics such as morphine and meperidine, in analgesic efficacy... with less likelihood of some of the extreme adverse effects produced by the opiates in general.

With Talwin there is a low incidence of respiratory depression, hypotension, urinary retention, and constipation.



In moderate to severe pain

Injectable **Talwin**®
brand of
pentazocine
(as lactate)

extremely effective for most patients

30 mg. 45 mg. 60 mg.

See important product information concerning warnings, adverse reactions, patient selection, prescribing and precautionary recommendations on last page of this advertisement.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), **45 mg.** (1½ ml.), and **60 mg.** (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp™—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* in boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10, 25, and 100.

Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for Injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

Winthrop

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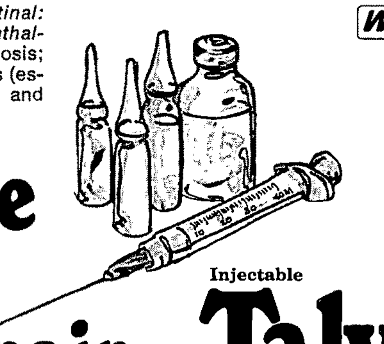


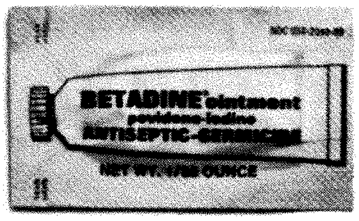
the unextreme injectable for serious pain

Injectable
Talwin®
brand of
pentazocine
(as lactate)

Microbicidal Power

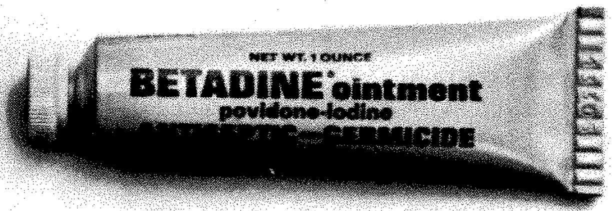
BETADINE Ointment

Now...a variety of sizes to meet a variety of needs

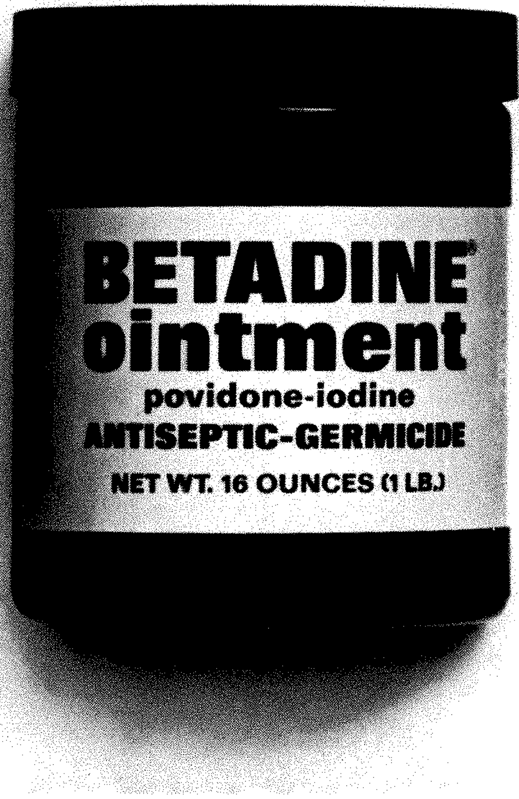


Packette 1/32 oz.
Single-use size for degerming small skin areas, as in the case of umbilical cord care and circumcision.

Packette 1/8 oz.
Single-use size for degerming small skin areas, as in the case of hyperalimentation and catheter care.



Tube 1 oz.
Multiple-use size for treating common skin infections... preventing infection in lacerations, abrasions and burns.



Jar 1 lb.
Heavy-use size for treating infected stasis ulcers... burns... extensive skin areas or prolonged treatment.

■ broad-spectrum microbicidal action—kills both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), fungi, viruses, protozoa and yeasts
■ virtually nonirritating... does not stain skin and natural fabrics
■ does not block air... site can be bandaged ... water-soluble, washes off easily... not greasy or sticky... exerts prolonged action

Purdue Frederick

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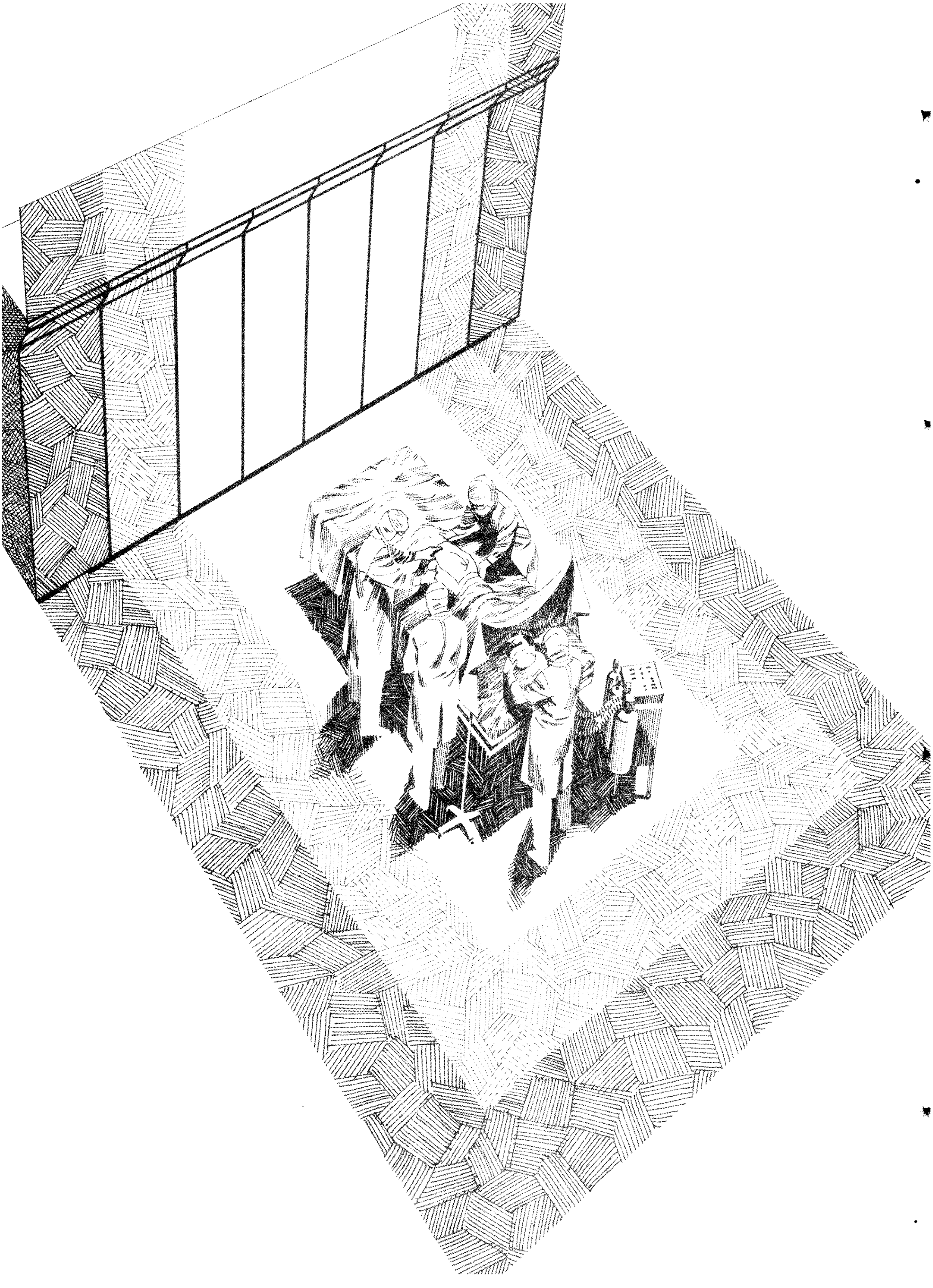
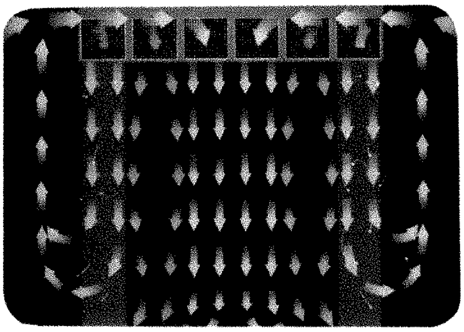
NORWALK, CONN. 06856 A7228 133673

BETADINE microbicides
Chosen by NASA



the Weber clean air system controls airborne contaminates without confining the surgical team.

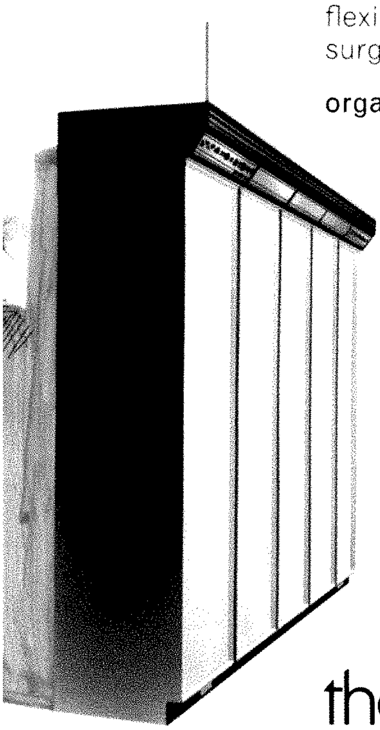


The Weber Horizontal Laminar Flow Clean Air System helps reduce airborne contamination by controlling the flow of ultra clean air over the surgical site. This control, plus the Weber's modular construction, permits total design flexibility and freedom for the surgical team.

organism count is near zero

While there is still no established relationship between clean air and infection rates, the reduction of bacterial contamination tends to parallel reduction of dust particle contamination.*

The Weber System can assist your sepsis control by bringing the level of viable airborne contamination (.3 microns and larger) down to between zero and 0.1 organisms per cubic foot.

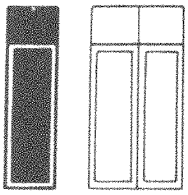


a unique flow principle

The Weber System uses a unique, patent-pending principle called Delta V to control the air flow. This minimizes entrainment of any ambient air particles into the stream of filtered air over the surgical site while reducing the "coning" effect of the clean air column found in conventional laminar air flow systems.

no confining structures

The Weber System is made up of free-standing modules which attach together. This allows you to determine the exact size of the system you need. And you can use the Weber System as a wall-less unit, or add optional side panels at any width.



Either way, you and your team can move freely, surrounded by a stream of clean, filtered air.

a detailed film is available

We have prepared a detailed film to assist you in your evaluation of the new Weber Horizontal Laminar Flow System. If you would like to see it and receive a detailed brochure, please call your Zimmer man.

the Weber
horizontal laminar flow clean air system

ZIMMER · USA
Warsaw, Indiana 46580

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*Irwin R. Krasnoff, M.P.H., *Aspects of Vertical Laminar Flow as a Hospital Contamination Barrier:* University Hospital, The University of Michigan Medical Center, 1969.

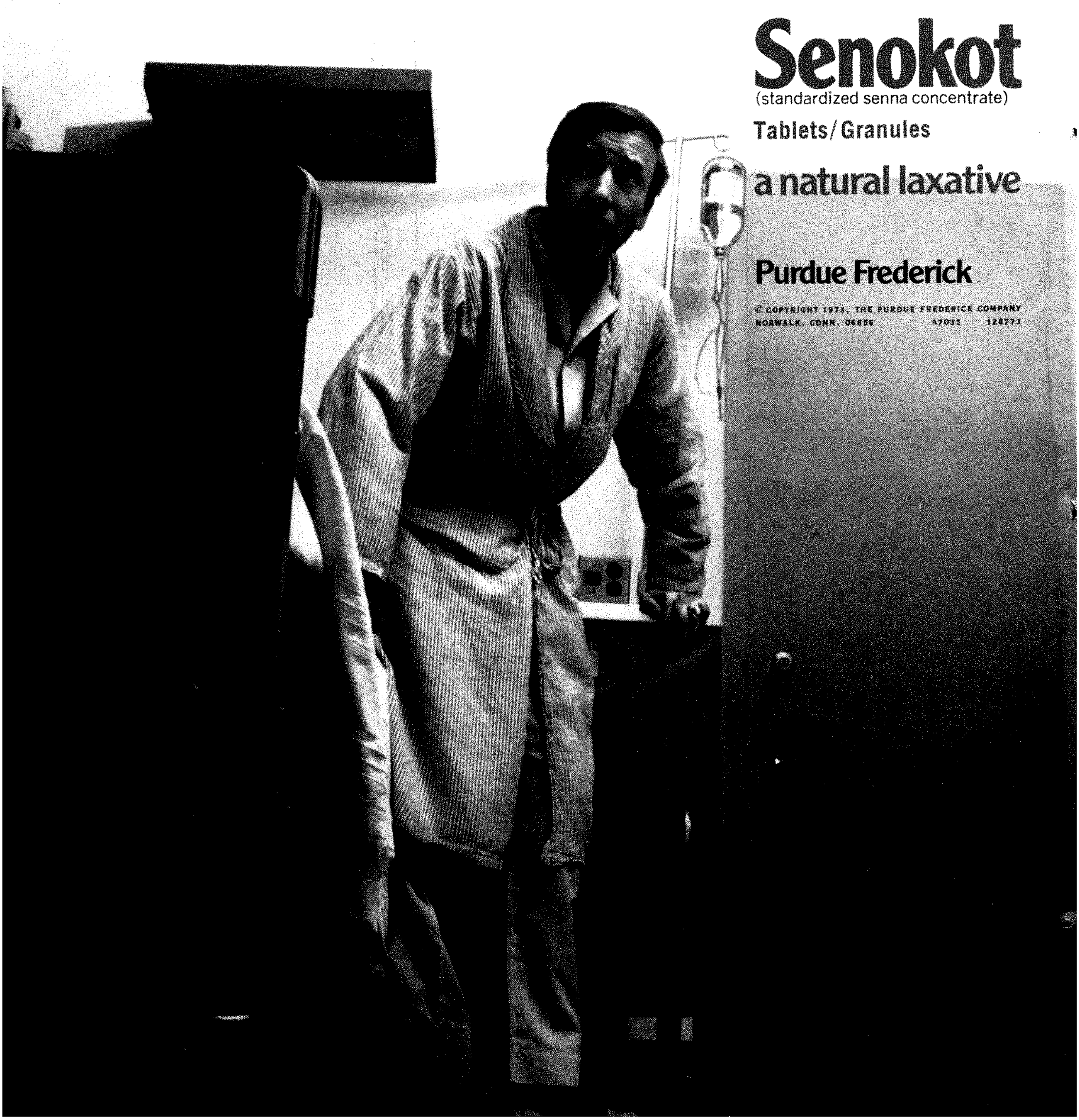
situation: constipation: laxation:

Post-operative . . . recent surgery . . . still confined to bed . . . or restricted ambulation . . .

Constipating analgesics and sedatives . . . immobilization . . . reduced food and fluid intake . . . constipation common . . . fecal impaction a threat to be avoided . . .

Gentle and predictable with colon-specific SENOKOT Tablets/Granules. Virtually free from side effects in appropriate dosage.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4, 8 and 16 ounce (1 lb.) canisters.



Senokot
(standardized senna concentrate)
Tablets/Granules

a natural laxative

Purdue Frederick

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T.E.D.

anti-embolism stockings

Thromboembolism, and its frequent sequelae pulmonary embolism, continues to be a major problem for the active adult suddenly confined to bed. The legs are a primary generating area for thrombi. With relaxation of the leg muscles, and subsequent expansion of the venous system in the legs, stasis develops. The proper amount of graduated, circumferential compression causes the velocity of the blood flow to increase in the deep veins of the legs. This is important in the prophylaxis of thromboembolism.

Kendall offers the highest quality in construction to assure correct compression. The T.E.D. stocking also comes in the most complete line of sizes and styles—thigh length, knee length, both with inspection toe. Only with T.E.D. stockings can each patient be given optimum fit for safe, proper wear.

Ask your Kendall salesman to explain proper measurement for correct sizing and application of the T.E.D. stocking. He also has reprints of articles on pulmonary embolism and an In-Service Program which gives the complete story of T.E.D. Anti-Embolism Stockings.

Remember, T.E.D. is a registered trademark of the Kendall Company anti-embolism stockings and... Kendall Sets the Pace.

Contraindications: In patients with open ulcers, severe arteriosclerosis and other ischemic vascular diseases, and massive leg edema with imminent pulmonary edema from congestive heart disease. Any signs of irritation or redness of the skin should be carefully noted.

Caution: Federal law restricts this device to sale by or use on the order of a physician.

KENDALL
sets the pace

THE KENDALL CO. Hospital Products Division
309 W. Jackson Blvd. Chicago, Illinois 60606

☐ I'd like more information about TED stockings.

☐ I'd like copies of medical journal articles dealing with thromboembolic disease.

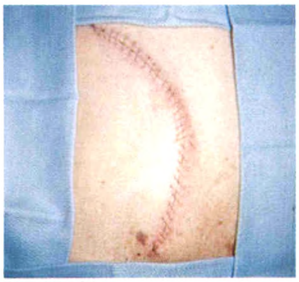
name

hospital affiliation

address

city state zip

CURITY®
wet dressings


Infected
Suture Wounds

Infiltrated I.V.'S

Decubitus Ulcers

Debridement

Easy Aseptic Application

Curity® wet dressings provide sterile, moist heat therapy for many medical conditions. Each sterile dressing comes pre-moistened, in an individual foil package designed for aseptic opening and application. And Curity gives you a choice of water or normal saline solution.

The cumbersome procedure for preparing sterile wet dressings is eliminated. The Curity system saves time, facilitates sterile technique and provides hot moist dressings from the heat lamp in just minutes.

a Better System of ►
Complete Wound Management

This system incorporates what we call the "Functional Dressings Principles" into a comprehensive program of wound care. Your Kendall representative is eager to present this system to you through a highly informative audio-visual in-service program. Contact him today or write The Kendall Company, 309 W. Jackson Blvd., Chicago, Illinois 60606.

KENDALL
sets the pace

New from SK&F...

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

(lyophilized)

Parenteral Cephalosporin Antibiotic

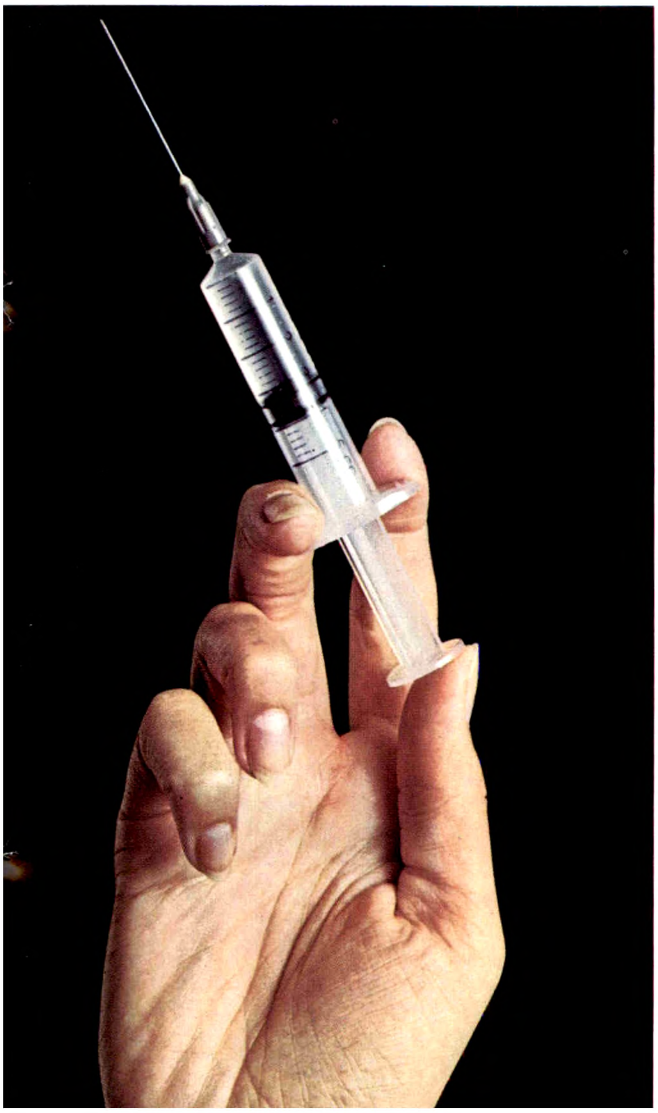
Injection: 250 mg., 500 mg. and 1 gram

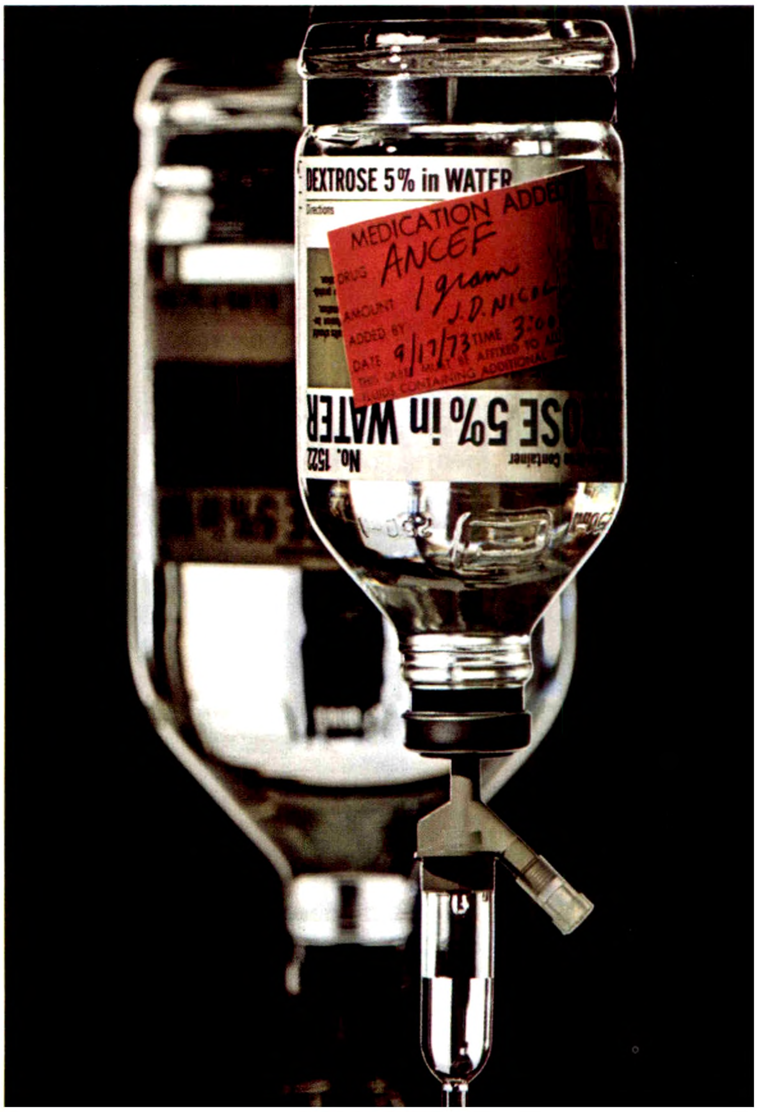
Please see brief summary of prescribing information on last page of this advertisement.

I.M.

Offers the convenience of I.M. or I.V. administration.
Pain on injection is infrequent with 'Ancef'.

I.V.





New from SK& ...

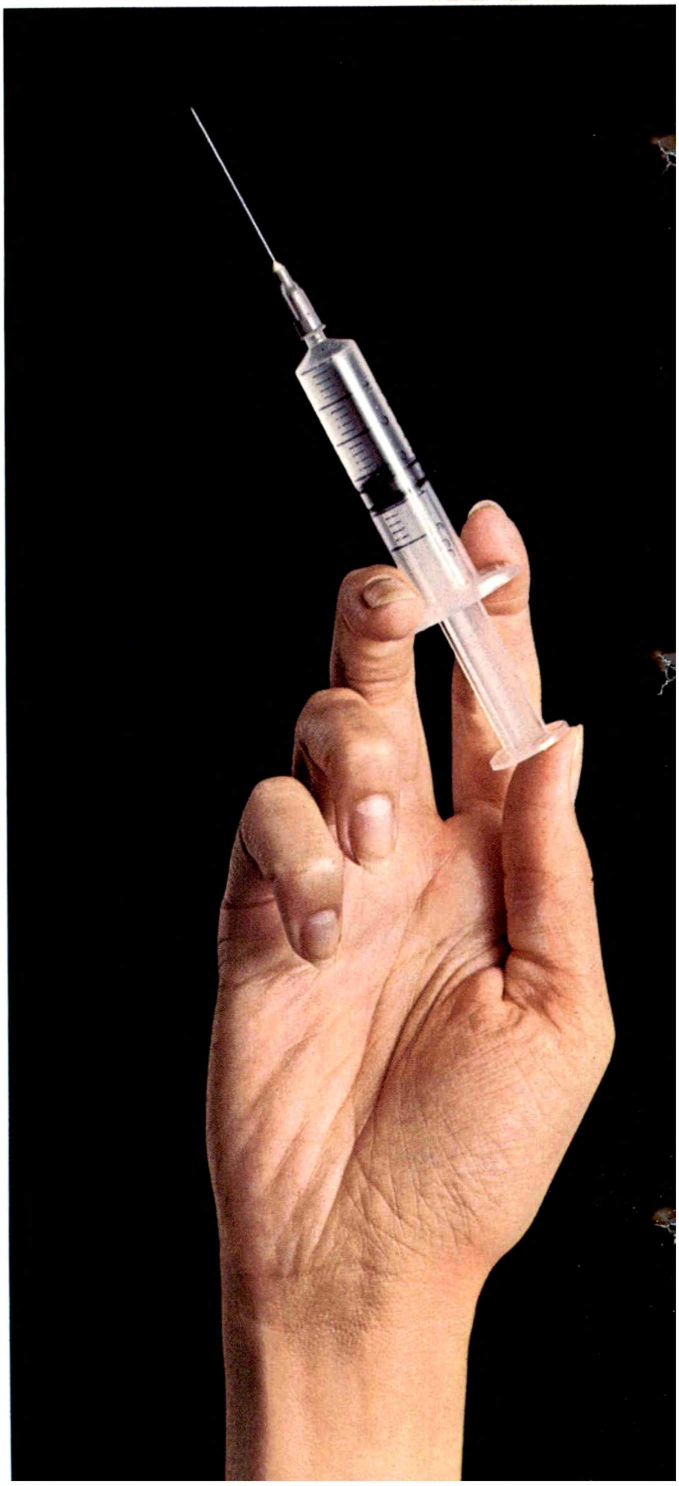
ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

(lyophilized)

I.M.



By either route...

'ANCEF' produces high blood levels.

(In a 3-part crossover study in 60 adult male volunteers, following a 500 mg. I.M. injection, a serum level of 36.8 μg./ml. was achieved at 1 hour; a level of 3.0 μg./ml. was still maintained at 8 hours.)

'ANCEF' Indications

Respiratory tract infections due to *D. pneumoniae, Klebsiella* species, *H. influenzae, S. aureus* and group A beta-hemolytic streptococci.

Genitourinary tract infections due to *E. coli, P. mirabilis, Klebsiella* species and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *S. aureus,* group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus.*

Septicemia due to *D. pneumoniae, S. aureus, P. mirabilis, E. coli* and *Klebsiella* species.

Endocarditis due to *S. aureus* and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

'ANCEF' is bactericidal against the following organisms *in vitro*:

Staphylococcus aureus
(penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci
(many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole-positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to 'Ancef'.

I.V.

ANCEF® brand of **sterile cefazolin sodium**

has produced no nephrotoxicity in extensive clinical trials.

(Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.)

Adverse Reactions

Adverse reactions reported in the clinical trials included: pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of adverse reactions associated with 'Ancef' therapy please see brief summary of prescribing information on last page of this advertisement.

'ANCEF' Clinical Efficacy

Site of Infection	Number of Patients	% "Good" or "Excellent" Response*
Respiratory Tract	377	93%
Genitourinary Tract	544	93%
Skin and Soft Tissue	122	84%
Blood and Lymph	69	81%
Bone and Joint	35	80%
Miscellaneous and Multiple Site	34	85%

The preceding results were collected from identical clinical protocols with comparable criteria of efficacy.

*Excellent: Initial improvement at 1-3 days with maximum improvement between 3-7 days. Good: Initial improvement at 2-4 days with maximum improvement between 4-10 days.

See following page for a brief summary of prescribing information including contraindications, warnings, precautions and dosage.

New from SK&F...

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM (lyophilized)

Before prescribing, see complete prescribing information in SK&F literature.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro*:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)
Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae — *Klebsiella* species
Escherichia coli — *Enterobacter aerogenes*
Proteus mirabilis — *Hemophilus influenzae*

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Diplococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Diplococcus pneumoniae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'ANCEF' IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for mild gram-positive infections is 250 mg. to 500 mg. of 'Ancef' every 8 hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every 8 hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 gram of 'Ancef' every 6 to 8 hours. 'Ancef' has been administered in dosages of six grams per day in serious infections such as endocarditis. 'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.) 60% of the normal daily dose given in divided doses q12h should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.) 25% of the normal daily dose given in divided doses q12h should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.) 10% of the normal daily dose given q24h should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dose may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories, Division of SmithKline Corp.,
Philadelphia, Pa. 19101

Researches on the Cause of Burn Hypermetabolism

WILLIAM A. NEELY, M.D., ANTHONY B. PETRO, M.D.,
GARLAND H. HOLLOMAN, JR., Ph.D., FRED W. RUSHTON, JR., M.D.,
M. DON TURNER, Ph.D., JAMES D. HARDY, M.D.

From the Department of Surgery,
University Medical Center, Jackson, Mississippi

THE QUESTION of the cause of burn hypermetabolism continues to be controversial to investigators working in this field. Hardy, *et al.*,[5] in 1953 pointed out the large insensible water losses in severely burned patients. This loss through the skin was found to be quite large and was thought to be greatest initially, subsiding somewhat as an eschar was allowed to form. Moyer[7] has pointed out the increased heat necessary to evaporate this water. Lieberman and Lansche[6] showed an increased metabolic rate in burned rats and attributed this increased rate to evaporative water loss. Caldwell[3] has shown an increased metabolic rate in burned rats and has found a high correlation with evaporative water loss. In other words, he could quantitatively account for the excess hypermetabolic calories as those necessary to evaporate the excess insensible water.

Gump and Kinney[4] have verified the high caloric loss of burns, but have cast doubt that evaporative water loss could quantitatively account for all of the increased heat production. Zawacki[10] further questioned the stoichiometric relationship between excess metabolism and water loss. He found that covering patients with an impermeable film did not decrease metabolic rates. However, he studied the patients for only six minutes.

To try to reconcile these apparently opposing views, we have designed the following experiments in which we have employed a continuous computerized, indirect calorimetry system that is capable of great accuracy and speed of processing data.

Methods

The system consists of three basic units: instrumentation, computer, and program. These will be described somewhat in detail.

The instrumentation is essentially that described by Caldwell[3] with certain modifications to allow computer interfacing (Fig. 1). Air is drawn from a canopy, similar to that described by Kinney,* at a rate such that all leaks are inward and total expired gases are contained within the total sample. For convenience the flow through the canopy is set at 60 liters per minute. The pump used to provide the negative pressure to cause this flow is an ordinary vacuum cleaner pump, the speed of which is set roughly by an autotransformer. Fine adjustment is provided by the valve shown in Fig. 1. Thus all expired air plus an excess of room air is led to the computer room.

An in-line Singer dry test meter measures the flow by sending an electrical pulse to the computer for each liter of gas passing the meter. Down line from the measuring instrument, a gas sample is pumped to a Drierite column to remove all significant water vapor, then divided through two rotameters to a Beckman paramagnetic oxygen analyzer and a Beckman infrared carbon dioxide analyzer. The output of these instruments, a voltage proportional to oxygen and carbon dioxide concentration, is fed to the computer.

Submitted for publication April 6, 1973.

Supported by U.S.P.H.S. Grant No. GM 17961 and National Institutes of Health Grant No. RR00626.

* Personal communication.

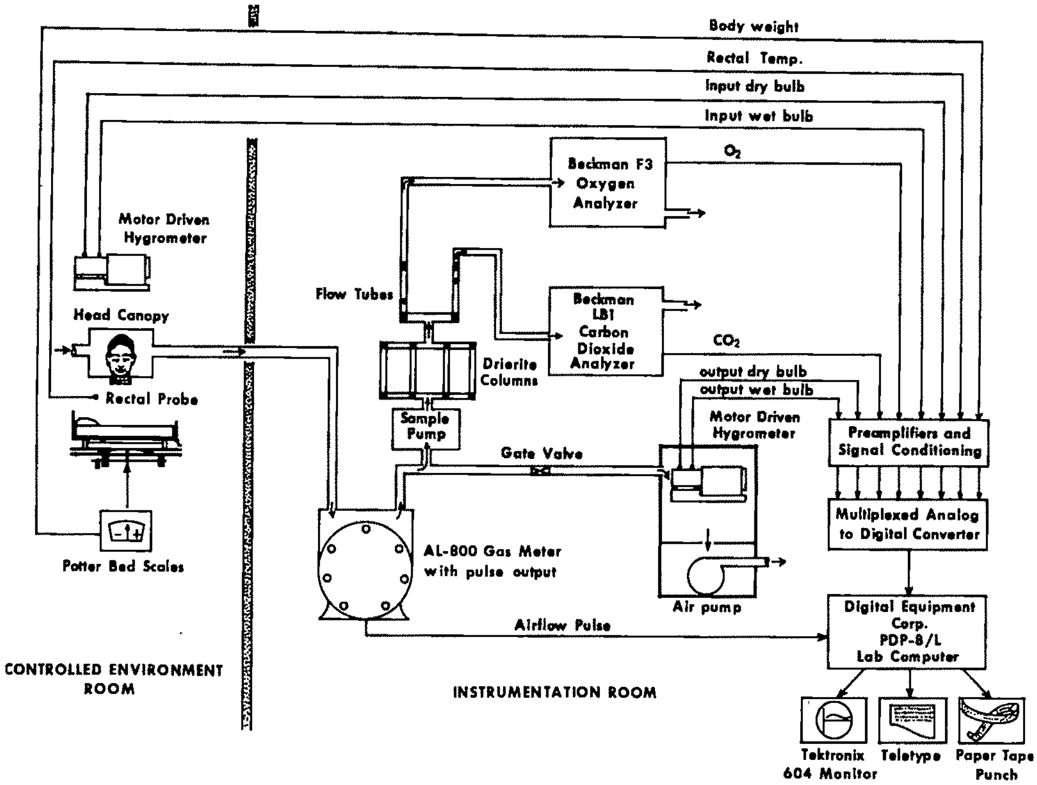
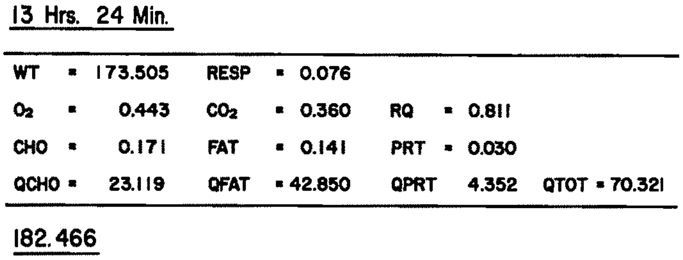


FIG. 1. Schema showing apparatus for indirect calorimetry with on-line programmed data processing. This schema is somewhat modified from that originally used (Holloman, G. H., *et al.* J. Appl. Physiol., in press).

The data processor is a Digital Equipment Corporation PDP-8 machine with a 16 channel analogue to digital converter which provides the computer with the basic data from the analyzers. Suitable solid state operational amplifiers are utilized to condition the analog signals to the computer's range of voltages. To summarize, the computer is supplied with three basic signals: volume, oxygen concentration, and carbon dioxide concentration.

The program processes the oxygen concentration, carbon dioxide concentration, and flow (computed from dry test meter pulse) into a readout each minute (corrected for barometric pressure and temperature) of oxygen consumption, carbon dioxide elimination, respiratory quotient, grams of carbohydrate, fat, and protein, and energy produced due to each foodstuff and total energy produced in watts/square meter (Fig. 2). (Protein is computed from hourly urinary nitrogen which is typed into the computer.) The equations of Boyd[2] are used by the computer to solve for the above parameters.

The patient is placed upon a bed supported by a Potter scale, the output of the scale being fed to the computer, allowing printout of weight loss due to insensible water loss each minute. A plastic wrapping is placed upon the bed and wrapped about the patient.



```
13 Hrs. 24 Min.

WT   =  173.505   RESP  =  0.076
O2   =    0.443   CO2   =  0.360   RQ   =  0.811
CHO  =    0.171   FAT   =  0.141   PRT  =  0.030
QCHO =   23.119   QFAT  = 42.850   QPRT    4.352   QTOT = 70.321

182.466
```

FIG. 2. Format for computer printout showing weight change (g./min.) due to insensible water loss; O_2 consumption (ml./min.); CO_2 elimination (ml./min.); RQ; carbohydrate, fat, and protein utilization (g./min.); and rate of energy production due to each foodstuff (watts/m².).

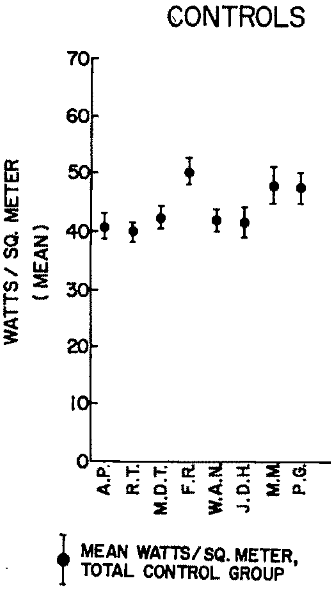


FIG. 3. Rate of energy production in normal controls (mean watts/m².).

The canopy is placed about the head, the computer started and a steady metabolic state is obtained. When there is a steady state, the plastic material is removed and another steady state attained. Frequently the procedure is reversed, that is, the patient is uncovered first. Ambient temperature is 24°C. and at other times 30°C. Rectal temperature is measured at 15-minute intervals. Hourly urinary nitrogen is measured from hourly to 24 hour urine samples analyzed by a Coleman nitrogen analyzer. This total nitrogen value is typed into the computer.

Results

The output of the computer is displayed in the format shown by Fig. 2. The printing interval may be changed at will. The scales print out weight in grams each minute. (This can be set to zero as desired.) The oxygen consumption and carbon dioxide elimination are shown in liters/min. Carbohydrate, fat, and protein utilized are shown in grams/min. The bottom line is shown as watts per square meter but calories may be printed out at will.

Eight normal patients were studied and the results are displayed in Fig. 3. Patient AP was utilizing fuel at the rate of 40.9 ± 2.4 watts per square meter; subject RT, 40.1 ± 1.7 watts per square meter; subject MDT, 42.7 ± 2.1 watts per square meter; subject FR, 50.1 ± 1.9 watts per square meter; subject WAN, 42.0 ± 2.2 watts per square meter; subject JDH 41.9 ± 2.6 watts per square meter; subject MM, 48.4 ± 3.2 watts per square meter; and subject PG, 47.9 ± 2.7 watts per square meter. The mean of the total control group was 45.5 ± 4.2 watts per square meter.

Figure 4 shows the results of several individual burned patients studied covered with sterile plastic wrapping, uncovered, and recovered with wrapping. Standard deviation is indicated by the vertical line terminated by a dash. The solid lines connect consecutive studies. Rectal temperature is recorded beside each study. It should be noted that mean watts/square meter is much higher than the normal values mentioned above. There was an 18 to 59% increase in energy production when the patients were uncovered with no significant change in body temperature.

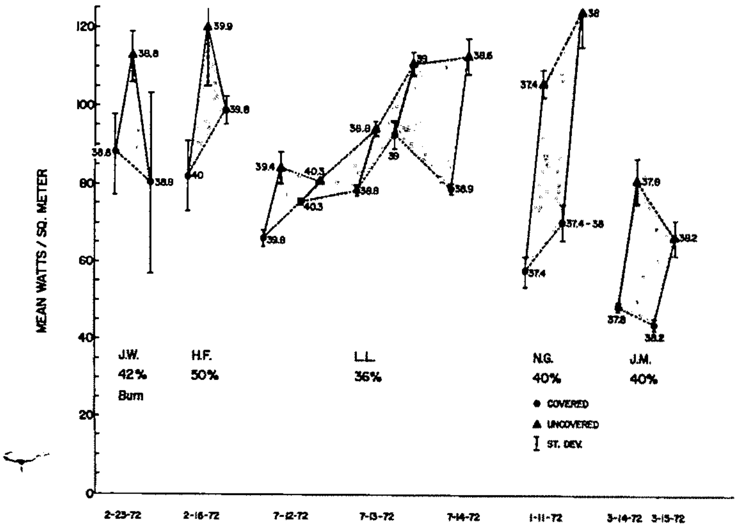


Fig. 4. Rate of energy production in burned patients, showing rise when plastic wrapping is removed.

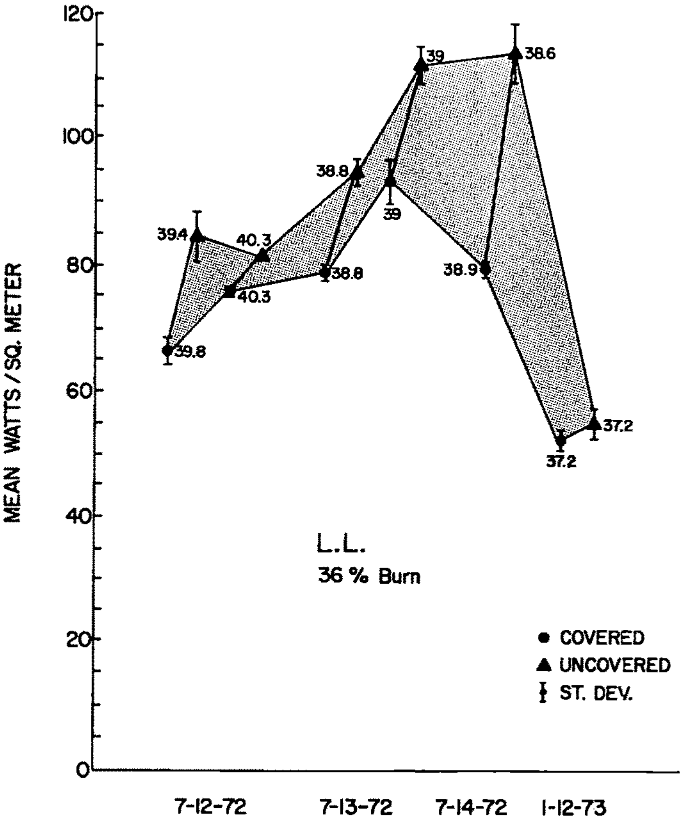


Fig. 5a. Rate of energy production in burned patients during the early phase, convalescent phase, and recovery phase. Note that the metabolic rate decreases as the patient approaches recovery.

Figures 5a, 5b, and 5c show the energy production of three patients studied from early injury to healing. Here

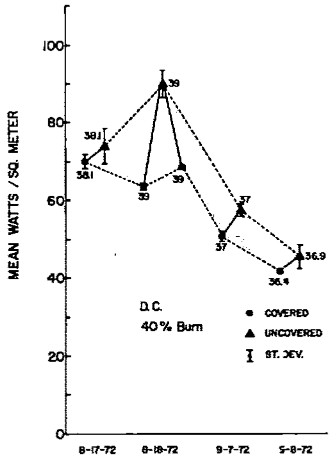


Fig. 5b. See legend for Fig. 5a.

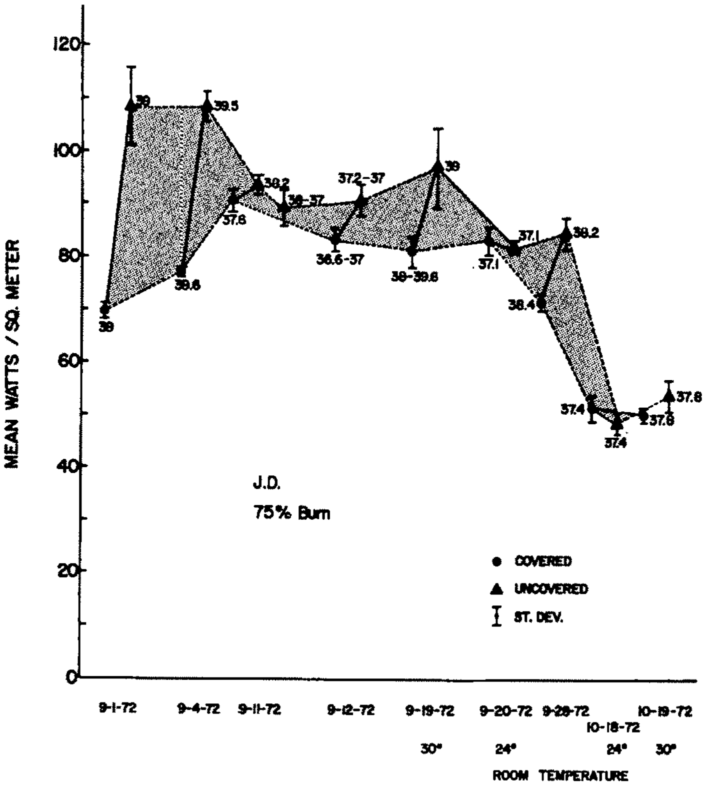


FIG. 5c. See legend for Fig. 5a.

again the covered metabolic rate was much higher than normal control, and there was a large rise in energy production when the patient was uncovered. The temperatures of patients L. L. and D. C. were elevated when covered. However, in patient J. D. (Fig. 5c) many covered and uncovered temperatures were in the normal range.

Discussion

It seems inescapable that our patients suffered from a high basal metabolic rate even when covered with a plastic material that is known to prevent evaporative water loss. There is no doubt that this rate is increased by uncovering and allowing evaporative water loss to occur. There are those, however, who will contend that the high basal rate was due directly to the high body temperature. This could explain the high heat production of patients L. L. and D. C., 36% and 40% burns respectively. However, this could not be the explanation for the high metabolism of patient J. D., a 75% burn. Many of the elevated heat production determinations were obtained at normal body temperatures. It should be pointed out here that all three patients recovered and the last studies were done after recovery. The data on this last patient indicated that the hypermetabolism of severely burned patients may not be entirely explained by evaporative water loss or temperature elevation. Kinney[4] has alluded to additional mechanisms and Clowes[9] has already shown the hypermetabolism of peritonitis. The explanation could be the elevation of temperature that nearly always accompanies peritonitis. We have shown that patients in septic shock have elevated cardiac output and oxygen consumption, even just before death.[8]

We believe that there are additional mechanisms of increased heat production in these patients and that it may be due to high catecholamines as Birke[1] found in his hypermetabolic thermally burned patients.

Summary

Studies in seven burned patients have demonstrated that these patients are hypermetabolic and become more so when completely exposed and less so when covered with a waterproof plastic material. Most of these patients also had elevated body temperatures. One patient remained normothermic during most of the study and was still hypermetabolic. All patients returned to normal metabolic rate after recovery. This study suggests that the hypermetabolism of the burned patient is caused by factors in addition to evaporative water loss.

References

1. Birke, G., Carlson, L. A., von Euler, U. S., Liljedahl, S.-O. and Plantin, L.-O.: Studies on Burns. XII. Lipid Metabolism, Catecholamine Excretion, Basal Metabolic Rate, and Water Loss During Treatment of Burns with Warm Dry Air. Acta Chir. Scand., 138:321, 1972.
2. Boyd, W. C.: Error in Calibration of Commercial BMR Machines. J. Appl. Physiol., 6:711, 1954.
3. Caldwell, F. T., Hammel, H. T. and Dolan, F.: A Calorimeter for Simultaneous Determination of Heat Production and Heat Loss in the Rat. J. Appl. Physiol., 21:1665, 1966.
4. Gump, F. E. and Kinney, J. M.: Caloric and Fluid Losses through the Burn Wound. Surg. Clin. N. Amer., 50:1235, 1970.
5. Hardy, J. D., Neely, W. A., Wilson, F. C., Jr., Milnor, E. P. and Wilson, H.: Fluid Kinetics Following Thermal Burns in Man; Preliminary Report. Surgery, 34:457, 1953.
6. Lieberman, Z. H. and Lansche, J. M.: Effects of Thermal Injury on Metabolic Rate and Insensible Water Loss in the Rat. S. Forum, 7:83, 1957.
7. Moyer, C. A.: The Metabolism of Burned Mammals and its Relationship to Vaporizational Heat Loss and Other Parameters. *In* Research in Burns. Washington, D. C., American Inst. Biol. Sci., and Philadelphia, F. A. Davis Company, 1962.
8. Neely, W. A., Berry, D. W., Rushton, F. W., Jr. and Hardy, J. D.: Septic Shock: Clinical, Physiological, and Pathological Survey of 244 Patients. Ann. Surg., 173:657, 1971.
9. Rubin, J. W. and Clowes, G. H. A., Jr.: Cardiovascular Stresses in Surgery. Surg. Clin. N. Amer., 49:489, 1969.
10. Zawacki, B. E., Spitzer, K. W., Mason, A. D., Jr. and Johns, L. A.: Does Increased Evaporative Water Loss Cause Hypermetabolism in Burned Patients? Ann. Surg., 171: 236, 1970.

Anaplastic Carcinoma of the Thyroid

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Although a great amount of information has accumulated on well-differentiated cancers of the thyroid, information about undifferentiated or anaplastic carcinoma of the thyroid is scant. Only a relatively few papers concerning this lethal form of thyroid cancer are found in the literature. This report is an analysis of the cases of anaplastic thyroid carcinoma seen at the University of Minnesota Hospitals (UMH) and the Minneapolis V-A Hospital (VAH).

Material and Methods

The charts of all cases of anaplastic thyroid carcinoma seen until July 1971 were reviewed. Thirty-one cases were found. The histology of these tumors was reviewed to assure accuracy of classification. Follow-up information was obtained from outpatients' visits, from the patients' physicians and by correspondence with the patients.

Age and Sex

Of 25 patients seen at the UMH 13 were males and 12 were females, a ratio of about 1:1. This is in agreement with some reports[11,14] although most series report a 2:1 female to male ratio.[1,9,10] The six remaining patients were males seen at the VAH. The mean age of the patients fell in the 7th decade, with a range from 19 to 82 years.

Symptoms

The most frequent symptom was a reported mass in the neck. (Table 1). This was reported by 80% of the patients. Hoarseness, dysphagia, loss of weight and other symptoms indicating both local invasion or distant metastasis were present. The most common symptoms were due to involvement of the trachea, esophagus or vocal cords, and are indicative of direct extension. This is in contrast to those symptoms caused by the slowly growing well differentiated cancer of the thyroid. In this series only 3 patients were asymptomatic except for the presence of a thyroid mass.

The duration of symptoms before seeking medical advice was usually a few months. However, 3 patients had symptoms for only three weeks before seeking medical attention. Six of the 31 patients had a history of goiter ranging from 3 to 15 years. Five of these had no therapy for their goiter, and they sought medical advice because of a recent increase in size. The sixth patient had a goiter for 5 years and underwent thyroidectomy three and a half years prior to admission to our institution. Eighteen months later, however, he underwent a right radical neck dissection because of metastatic disease, and two months later he underwent X-ray therapy for a single lesion in the right lung. He was now admitted to the UMH because of hemoptysis of 5 months duration. One patient had a history of radiation to the neck region for a papilloma of the vocal cord.

Physical Findings

A thyroid mass was the most common finding (81% of cases); followed by other cervical findings indicating metastasis (79%), chest findings, and finding of distant metastasis. (Table 2). The thyroid mass varied in size from a single localized nodule to diffuse, irregular and massive enlargement of one or both lobes of the gland. Tracheal deviation, cord paralysis and an immobile mass were ominous, indicating direct extension of the disease. Only seven patients had no other findings except for the presence of a thyroid mass.

Laboratory Findings

Chest X-ray was extremely helpful. When first seen in this institution, 16 patients (53%) had multiple lung

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TABLE 1. *Symptoms of Patients with Anaplastic Thyroid Cancer in Descending Order of Frequency*

Symptom	No. of Patients	Per cent
Reported Mass	24	80
Hoarseness	16	53
Dysphagia	13	43
Loss of Weight	12	40
Dyspnea	9	30
Weakness	3	10
Hemoptysis	3	10

metastasis, 43% had a mediastinal mass, 7% had a pleural effusion and 7% had bony metastases in the ribs. Only 3 patients (10%) had normal chest X-ray on admission, whereas the rest (90%) had some evidence of metastasis on chest X-ray. Metastatic bone survey was done in ten patients and was negative in all (excluding the two cases found to have bone metastasis on routine chest X-ray). Barium swallow was done in 7 patients with history of dysphagia and it was positive in all seven cases, demonstrating displacement or partial obstruction of the esophagus.

None of these patients had clinical hypothyroidism. Thyroid function studies reflected the clinical impression. PBI was done in 10 cases and it was normal in 9. ^{131}I uptake was done in 16 cases. It was normal in 9 (56%) and below normal in 7 cases (44%). Of the 12 patients who had thyroid scans 86% had demonstrated cold nodules or remarkably decreased uptake.

Method of Diagnosis

The diagnosis of thyroid cancer was suspected clinically in 30 cases, before any definitive diagnostic procedure was done. It was missed in one case, in which the symptoms were entirely non-specific and not related to the thyroid. This patient had a diagnostic laparotomy and removal of tumor-filled adrenal of unknown primary. Diagnosis was made at post mortem examination by finding undifferentiated carcinoma of the thyroid.

TABLE 2. *Physical Findings in Descendings Order of Frequency*

Finding	No. of Patients	Per cent
Thyroid mass	25	81
Unilateral	16	
Bilateral	9	
Cervical findings	24	79
Tracheal deviation	8	
Cervical adenopathy	8	
Horner's syndrome	2	
Vocal cord paralysis	4	
Tonsillar mass	1	
Prominent neck veins	1	
Chest findings (consolidation, pneumothorax)	8	26
Distant findings	6	20
Hepatomegaly	5	
Abdominal tumor	1	

TABLE 3. *Method of Establishment of Diagnosis*

Method of Diagnosis	No. of Patients	Per cent
Thyroidectomy	14	48
Simple thyroid mass biopsy	11	35
Postmortem examination	3	10
Esophagoscopy and biopsy	1	2
Salpingo-oophorectomy	1	2
Tonsilar biopsy	1	2

The diagnosis was established by biopsy of the thyroid, either excisional or simple in 83% of the cases, biopsy of metastasis in 6% and at post mortem examination in 10% (Table 3). Laryngoscopy and biopsy was utilized in two cases of suspected vocal cord invasion and it was positive in both.

Therapy

The method of treatment varied, depending primarily on the stage of the disease and the general condition of the patient, and whether any primary therapy was administered elsewhere before the patient was seen in our institution. The treatment employed was surgical in 6 cases, radiotherapy alone in 1 case, a combination of radiation and chemotherapy in 6 cases, and a combination of surgery plus radiotherapy and/or chemotherapy in 17 cases (Table 4). One patient died before any therapy was initiated.

Surgical treatment was utilized in 23 cases (Table 5). Of these 23 operations, 6 were tracheostomies alone. The rest involved a variety of procedures. Four patients were operated on elsewhere, and were referred to the University Hospitals for radiotherapy. In our institution therefore, thirteen thyroid operations were done. In none of these operations, however, was it felt that the procedure was potentially curable. In all thirteen cases tumor was left behind, either because it was technically impossible to remove or because it involved one or more vital structures. Extension of tumor was reported to involve one or both recurrent nerves, the esophagus, the trachea, the thyroid cartilage, the carotid vessels, the strap muscles of the neck, the vagus nerves, the jugular veins, and the superior mediastinum.

In all surgical procedures as much tumor as possible was removed to facilitate tracheal decompression and in

TABLE 4. *Method of Treatment: 30 Cases of Anaplastic Thyroid Carcinoma*

Method of Treatment	No. of Patients
Surgery alone	6
Surgery and radiotherapy and/or chemotherapy	17
Radiotherapy alone	1
Radiotherapy and ^{131}I and/or chemotherapy	6

a few cases tracheostomy was added. Radiotherapy was used either alone (one case) or in combination in 24 cases. The amount of radiation ranged from 3500 r to 6000 r given over several weeks. A variety of chemotherapeutic agents were used, such as, mustards, cytoxan, methotrexate, mithromycin and steroids.

Results and Follow-up

Two patients were lost to follow-up and are excluded. In the remaining 29 patients, the average survival from the onset of symptoms was 9.1 months, and the average survival after treatment was 5.3 months. Eleven patients survived for less than 6 months after onset of symptoms, and between 3 days and two months after treatment (Table 6). Ten patients lived between 6 and 12 months after onset of symptoms and 2 weeks to 6 months after treatment. Four other patients survived less than 1 year following treatment.

One patient lived 33 months after onset of symptoms and 32 months after treatment, and two patients lived for 36 months after appearance of symptoms, and 24 months after treatment. These three long-surviving patients had mixed tumor, consisting of both well-differentiated and anaplastic carcinoma. The significance of this feature will be discussed later.

No conclusions can be drawn from these results as to the superiority of any particular form of therapy. One of the 3 longest surviving patients had surgery alone, and the other two had a combination of surgical and radiation therapy. One of these had an end-on tracheostomy performed, removal of the major portion of the tumor, and closure of the proximal end of the divided tumor-involved trachea. Survival was not related to the stage of the disease, as these long-surviving patients had both local spread and distant metastasis at the time of treatment.

Pathologic Features and Causes of Death

No attempt was made to classify the tumors according to their specific cell characteristics such as spindle cell, giant cell or small cell cancers, because their lethal potential and overall prognosis did not differ. It is, however, very important to mention that eight of our patients had a mixture of well-differentiated cancer and anaplastic carcinoma. As an example, one of the patients who was not commented on in the results, lived for 12 years after operation at the age of 8 years for what was thought to be a well-differentiated embryonal tumor. She was then repeatedly operated on for metastatic disease in the neck, and the diagnosis in later years was indeed undifferentiated carcinoma of the thyroid. The patient died at the age of 20 from causes unrelated to the disease. This may represent a case of transformation[7,11,15] of a well-differentiated tumor into anaplastic cancer. Further evidence for transformation was found in two patients who originally had well-differentiated carcinoma on biopsies, and later died of anaplastic cancer. The concept of transformation was further supported by the correlation between old goiters and mixed anaplastic and well-differentiated tumors. Six of our patients had goiters for several years before the onset of symptoms. It is possible that undifferentiated cancer did not arise *de novo* in these patients, but rather it represented transformation from well-differentiated tumors.[7,11,15] This is based on the fact that three of the 6 patients had microscopic features of mixed tumors when they sought medical advice (Fig. 1).

TABLE 5. *Types of Surgical Procedures Used in 23 Cases Treated Surgically*

Surgical Procedures	No. of Cases
Hemithyroidectomy	7
Hemithyroidectomy plus radical neck dissection	4
Total thyroidectomy	2
Total thyroidectomy plus radical neck dissection	2
Partial thyroidectomy	2
Tracheostomy alone	6

At the time of treatment local spread of tumor was found in 28 cases and distant metastasis in 27. Table 7 shows the sites of metastases in descending order of frequency. Local spread accounted for most metastases, followed by lungs, liver, adrenals, distant nodes, kidneys, spleen, pleura and heart.

The most common cause of death was cachexia associated with widespread metastasis (45%) followed by respiratory obstruction from local spread of the disease (Table 8).

Discussion

Anaplastic carcinoma of the thyroid is an extremely lethal disease. The available treatment is ineffective and prognosis is poor. Expected survival does not exceed one year in the majority of cases. Our results are comparable to other reports.[1,6,11,14] No conclusion can be reached from the present study as to the treatment of choice, because the results were uniformly poor despite different

TABLE 6. *Survival Following Appearance of Symptoms and Treatment*

No. of Patients	Survival After Onset of Symptoms	Survival After Treatment
11	Less than 6 months	3 days—2 months
10	6–12 months	2 weeks—6 months
1	14 months	8 months
2	12 months	10 months
1	13 months	11 months
1	33 months	32 months
2	36 months	24 months

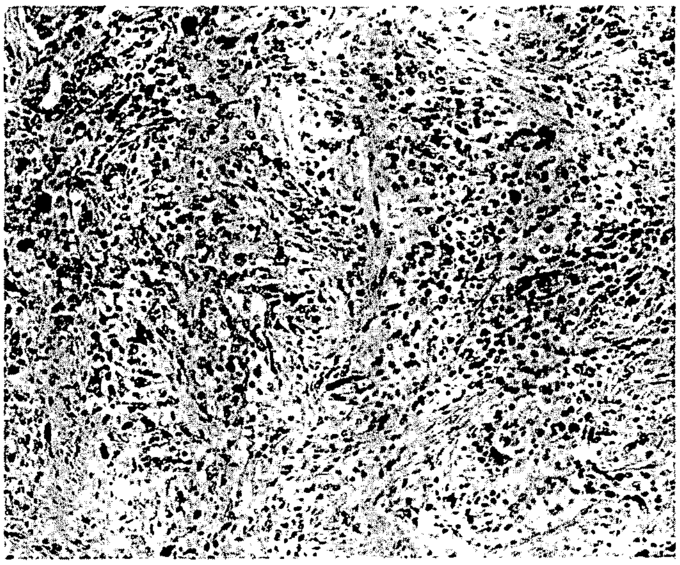

FIG. 1. Section through mixed thyroid tumor showing anaplastic cancer with evidence of gland formation in the left upper corner of the picture.

modes of therapy. The kind of treatment to be used should be individualized. It is reasonable to suggest, however, that a combination of surgical excision plus radiotherapy may offer the best results.[6]

A few authors reported good results with x-ray treatment alone. In a series of 44 patients Smedal and Meissner[12] reported 10 cases surviving 5 years and 13 patients surviving 3 years with X-ray treatment alone. They suggested that failure of radiotherapy in most cases was due to inadequate dose. Rafla[9] also reported three 5 year survivals, and 5 patients with 15 year survival! Surgery was performed in these patients to remove the bulk of the tumor and to relieve pressure symptoms. Radiation therapy was subsequently used in all patients. Ibanez *et al.*[11] in their post mortem series stressed the point that surgery is useful in controlling local disease. Of 11 patients who had no surgery, 9 died primarily of local disease, whereas of 6 patients who were treated originally by surgery only 2 died of local disease. In our series, about 45% died of local recurrence (Table 8).

TABLE 7. *Sites of Metastasis*

Local Metastasis		Distant Metastasis	
Site	No.	Site	No.
Trachea	14	Lungs	10
Regional nodes	12	Liver	9
Esophagus	8	Adrenals	8
Recurr. Laryng. nerve	4	Distant nodes	6
Carotid arteries	3	Kidneys	6
Larynx	2	Spleen	5
Tonsil	1	Pleura	4
		Heart	4
		Brain	3
		Bone	3
		Intestine	3
		Skin	2
		Ovaries	1

TABLE 8. *Causes of Death in 29 Cases Which Were Followed Up*

Cause of Death	No. of Cases	Per cent
Cachexia, widespread metastasis	14	45
Respiratory obstruction	10	32
Pneumonia	3	10
Hemorrhage from carotid artery erosion	1	3.25
Peritonitis	1	3.25
Lost to follow-up	2	6.5
	31 cases	100%

^{131}I does not seem to be useful, because these tumors do not take up iodine.[9] The use of chemotherapy was ineffective in our series, and it has not been used consistently as a means of treatment by others.

The concept of transformation of well-differentiated thyroid cancer into anaplastic carcinoma has been proposed by four previous papers.[7,10,11,15] This was also suggested by several of our cases. External radiation to well-differentiated tumors may play a role in transformation. Crile[4] and Silverberg[11] have warned against this danger. Despite the controversy that exists in the literature as to how radical the therapy of well-differentiated cancer should be,[2,3,5,8,13] it is reasonable to assume that complete eradication of well-differentiated carcinoma, will erase the possibility of transformation into anaplastic cancer.

Mixed tumors seem to have a better outlook than pure anaplastic cancers, as evidenced by our 3 longest survivors. This corroborates the report of Silverberg.[11]

Summary

Thirty-one cases of anaplastic carcinoma of the thyroid were seen at the UMH and the VAH of Minneapolis. Diagnosis was suspected clinically in 30 cases and it was established by biopsy of the primary or metastases in 28 cases.

None of the patients was considered to have curative disease at the time of treatment, despite relatively short periods of symptoms in most patients. Surgery was used alone or in combination with radiotherapy and/or chemotherapy, but the method of treatment did not influence the outcome of the disease. This type of cancer was uniformly fatal and only three patients survived more than one year from the time of treatment.

In eight of the 31 cases there was a mixture of anaplastic and well-differentiated tumors histologically, and it is suggested that some of the anaplastic cancers represent transformation from well-differentiated tumors.

Complete eradication of well-differentiated tumors by aggressive surgical treatment seems indicated in order to prevent such transformation.

References

1. Beemer, R. K. and Baker, H. W.: Anaplastic Cancer of the Thyroid. Northwest Med., **69**:417, 1970.
2. Clark, R. L. Jr., White, E. C. and Russell, W. O.: Ann. Surg., **149**:858, 1959.
3. Crile, G.: The Fallacy of the Conventional Radical Neck Dissection for Papillary Carcinoma of the Thyroid. Ann. Surg., **145**:317, 1957.
4. Crile, G.: Endocrine Dependency of Tumors of the Thyroid. Am. J. Surg., **99**:533, 1960.
5. Crile, G.: Survival of Patients with Papillary Carcinoma of the Thyroid after Conservative Operations. Am. J. Surg., **108**:862, 1964.
6. Granner, D. K. and Buckwalter, J. A.: Poorly Differentiated Carcinoma of the Thyroid Gland. Surg. Gynecol. Obst., **116**:650, 1963.
7. Ibanez, M. L., Russell, W. D., Albores-Saavedra, Jr. and Lambertico, P.: Thyroid Carcinoma—Biologic Behavior and Mortality: Portmortem Findings in 42 Cases Including 27 in which the Disease was Fatal. Cancer, **19**:1039, 1966.
8. Noguchi, S., Noguchi, A. and Murakami, N.: Papillary Carcinoma of the Thyroid II. Value of Prophylactic Lymph Node Excision. Cancer, **25**:1061, 1970.
9. Rafla, S.: Anaplastic Tumors of the Thyroid. Cancer, **23**:668, 1969.
10. Shonds, W. C. and Gotling, R. R.: Cancer of the Thyroid: Review of 109 Cases. Ann. Surg., **171**:735, 1970.
11. Silverberg, S. G., Hutter, R. V. P. and Foote Jr., F. W.: Fatal Carcinoma of the Thyroid: Histology, Metastases and Causes of Death. Cancer, **25**:792, 1970.
12. Smedal, M. I. and Meissner, W. A.: The Results of X-ray Treatment in Undifferentiated Carcinoma of the Thyroid. Radiology, **76**:927, 1961.
13. Tollefsen, H. R. and DeCosse, J. J.: Papillary Carcinoma of the Thyroid. Recurrence in the Thyroid Gland after Initial Surgical Treatment. Am. J. Surg., **106**:728, 1963.
14. Woolner, L. B., Bearhs, O. H., Black, B. M., McConaley, W. M. and Keating, F. R.: Classification and Prognosis of Thyroid Carcinoma. Am. J. Surg., **102**:354, 1961.
15. Wychulis, A. R., Bearhs, O. H. and Woolner, L. B.: Papillary Carcinoma with Associated Anaplastic Carcinoma in the Thyroid Gland. Surg. Gynecol. Obstet., **120**:28, 1965.

Pentagastrin Stimulated Pepsin Secretion in Man and Dogs

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THERE HAVE BEEN MANY SUGGESTIONS that feeding does not stimulate pepsin secretin from Heidenhain (vagally denervated) pouches in dogs.[7,8] Recently we have shown that pepsin secretion from denervated fundic pouches in dogs cannot be stimulated either by endogenous gastrin or intravenous pentagastrin.[3] Pepsin secretion from these pouches responds well, however, to cholinergic stimuli or to secretin.[3] The behavior of pepsin in man following vagotomy is not clear. Various authors have presented evidence of a reduced response to pentagastrin after vagotomy.[4] In most of these instances, however, no attempt was made to eliminate the possibility that the observed pepsin response was due simply to the more effective delivery of pepsin by the marked increase in the volume of gastric secretion following pentagastrin.

The subjects for this experiment were 68 patients referred for gastric analysis to the gastroenterological units of the Belfast City and the Royal Victoria Hospitals, both in central Belfast, and nine symptomless volunteers and medical students, from Queen's University and the two hospitals, as controls. The recent post-vagotomy patients, ten in all, were studied on either the seventh or eighth day after selective vagotomy and pyloroplasty. All gave negative Hollander tests.[5] It was not possible to study males and females separately since the recent vagotomies were all males. In Figs. 2 and 3, therefore, only data from the males were used.

We were able to study only five old vagotomy patients, *i.e.*, a year or more post-operation. All were males.

Each of the recently vagotomized patients had a double lumen gastrostomy tube put in place at operation. One lumen led to a duodenal tube, the other drained the stomach and served as the collecting tube for these experiments. In every other case, a radio-opaque nasogastric tube was passed and sited radiologically (except in the case of the medical students). Subjects lay in the left lateral position and the tubes (nasogastric or gastrostomy) were subjected to continuous suction.

The residual fasting juice was removed and kept, then two 30 min. unstimulated collections were made. At this point 6.0 μg/kg of pentagastrin (Peptavalon ICI) was given subcutaneously. The secreted juice was collected continuously for the next 60 min. at 15 min. intervals. In the first five recent post-vagotomy patients the stomach was rinsed twice with 50 mls. of water after each collection including the residual sample. In these it was established that pepsin did rise following pentagastrin. In the remaining five, the rinse was omitted and all ten treated as a group since they behaved identically.

It was possible in only three instances to test the same patients both before and after vagotomy. Old successful vagotomies were difficult to come by because of the natural reluctance of the asymptomatic to return to hospital. The old vagotomy patients were from one to six years post-vagotomy. All were Hollander negative. Two of the five had had truncal vagotomy, the others selective.

Aliquots from each of the samples were titrated on collection to pH 7.0 using a Radiometer Titrimeter. The results are expressed as mEq of H^+ per 15 min. Pepsin was estimated using Anson's hemoglobin method.[1] The optical density of the trichloracetic acid supernate at 280 $\mu\mu$ was determined and expressed as tyrosine using

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a standard curve. The results are expressed as mg. of tyrosine liberated from the substrate, incubated for 10 min. at 37°C, by the gastric secretion per 15 min.

Largely on the basis of X-ray, but in a few cases on laparotomy or gastroscopy, the symptomatic patients were divided into the following groups: a) Visible crater —crater actually seen, b) Scarring—no crater seen but obvious duodenal scarring or distortion, c) Symptoms only—neither active ulcer nor scarring seen in two or more X-rays. By way of comparison with the patients four dogs were equipped with gastric fistulae after low thoracic bilateral vagotomy. The effect of graded doses of pentagastrin on the pepsin secretion by these was studied. The significance of differences was determined using the non-paired t test in the patients and the paired t test in the dogs. Ninety-five per cent probability was taken as the level of significance.

Results

The mean values for acid and pepsin per 15 min. in each collection irrespective of sex are shown in Figs. 1a & 1b. Pepsin secretion after pentagastrin rose obviously and significantly in the controls and in the patients. There was no significant difference between the recently vagotomized and the patients with active craters with respect to the peak or duration of responses of pepsin. The acid response to pentagastrin was significantly smaller in the recently vagotomized than in the active crater patients. Residual and resting pepsin and acid secretion was significantly higher in the patients with visible craters than in the controls.

In controls the acid and pepsin responses to pentagastrin were neither as intense nor as prolonged as in any of the symptomatic groups.

In Fig. 2 are shown the pepsin means of the two resting collections calculated as per 15 min. (collections 2 and 3) and the means/15 min. of the first three post-pentagastrin collections (collections 4, 5 and 6) obtained from the male controls and the males only in each of the patient groups. These are the samples which include the peak response in every subject. This procedure greatly reduced variability since peak secretion could occur almost randomly in samples 4, 5 or 6.

It can be seen that in every instance pentagastrin raised the pepsin output but the increase in the five old vagotomies is not different from the controls. The pepsin response in the recent vagotomies is much greater than that in the controls or old vagotomies but only insignificantly less than in the unoperated visible crater patients. The pepsin responses in the patients with scarring and in those with symptoms and no discernible ulcer were almost identical but significantly less than in the patients with visible craters if males and females were grouped together. Most of the female patients were in the symptoms but no visible ulcer group. When they were excluded it can be seen that the pepsins in this group were

Fig. 1a. & 1b. (1a) Mean output ± SE of pepsin per 15 min. collection in males and females. Ordinate Mg. of tyrosine liberated from hemoglobin by the juice secreted in each period. (1b) Mean output of H⁺ in mEq/15 ± SE in males and females. Ordinate mEq H⁺/15 min. In both figures the abscissa represents successive 15 min. collections or sample number except for 1 which is the residual sample. Numbers 2 and 3 were 30 min. samples but the results have been calculated as per 15 min. Pentagastrin, 6.0 μg/kg, was given at the arrow.

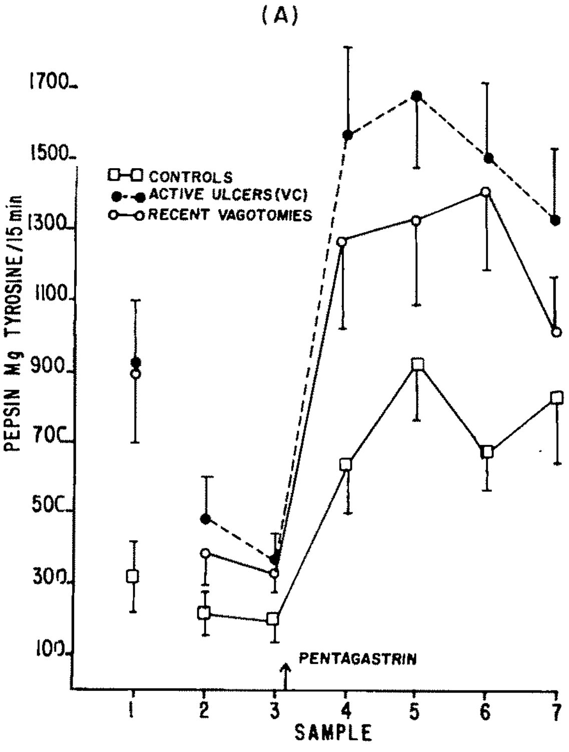

Fig. 1a.

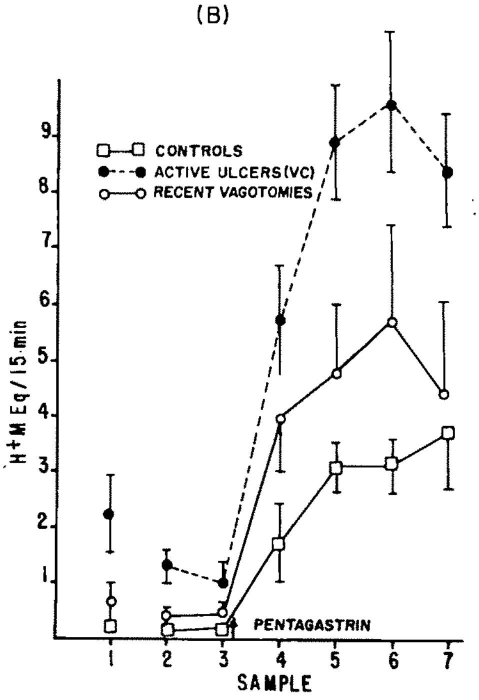

Fig. 1b.

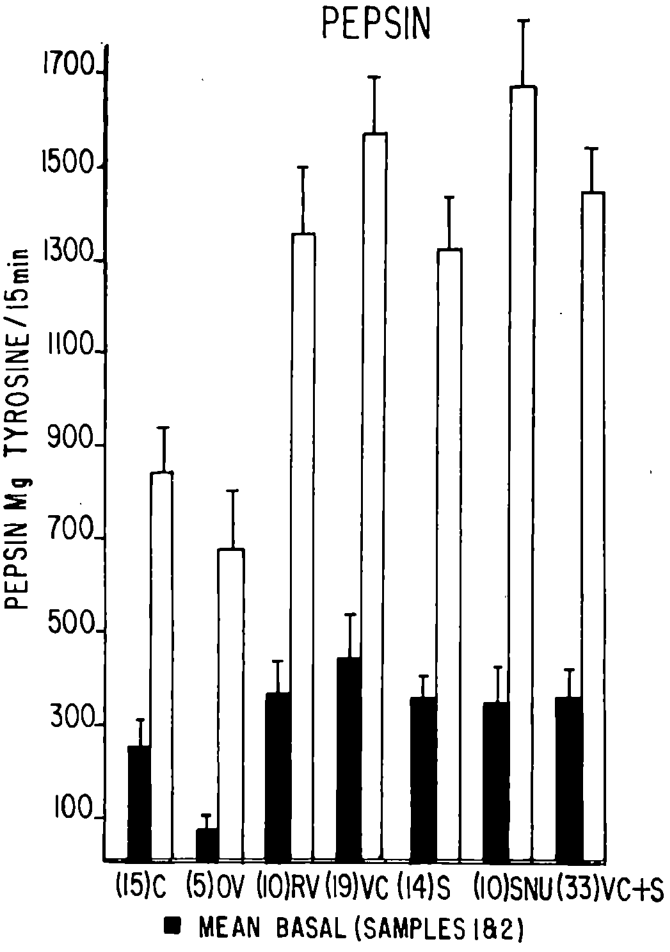

FIG. 2. Pepsin production per 15 min. before and after pentagastrin (males only). Basal bars are means of two resting collections (2 and 3) expressed as secretion per 15 min. ± SE. Pentagastrin bars are the means ± SE expressed as secretion per 15 min. of the first three post-pentagastrin samples (4, 5 & 6). C, controls; OV, old vagotomies; RV, recent vagotomies; VC, visible crater; S, duodenal scarring; SNU, symptoms but no ulcer. Numbers in parenthesis = number of subjects.

not significantly different from those in the males with visible craters. Acid secretion was, however, significantly higher in the latter. Unstimulated resting secretion was significantly higher in pepsin in the crater patients and recent vagotomies than in the controls or old vagotomies. Resting pepsin in the recent vagotomies was not less than in any of the unoperated patient groups.

It may be considered artificial to divide the symptomatic into groups largely on a radiological basis. If all the unoperated patients were treated as a single group, the means for pentagastrin stimulated and for basal acid and pepsin did not differ from those in the recent vagotomy group but did differ from the controls and old vagotomies. If we excluded those with symptoms but no radiological evidence of either a crater or scarring, then the stimulated acid secretion, but not the pepsin, became significantly larger in the unoperated than in vagotomy patients.

In Fig. 3 are shown the results for acid secretion. These are essentially the same as for pepsin except that acid is more drastically reduced by recent vagotomy than is pepsin but still not to the extent seen in old vagotomies. The acid response to pentagastrin is significantly less after recent vagotomy than in either the patients with visible craters or scarring.

As with pepsin the resting acids in patients with symptoms or recent vagotomies were significantly higher than in controls or old vagotomies. The results of the dog experiments are shown in Table 1. All four dogs were Hollander negative but a month earlier, before vagotomy, unstimulated pepsin levels and responses to all doses of pentagastrin were significantly greater. Here, again, there is a positive and a significant relationship between pentagastrin and pepsin up to the highest dose used.

Discussion

It is evident that pentagastrin does raise pepsin secretion following vagotomy. The essential difference, apart from species, between the present experiments and those in pouch dogs, is that vagotomized mucosa in the dogs resulted not from vagotomy as such but from the construction of Heidenhain pouches. There is evidence, including ours presented here, that in the intact vagotomized dog stomach pepsin secretion is stimulated by pentagastrin.[4] Perhaps in the pouch uninhibited sympathetic influence prevents the action of pentagastrin on the chief cell but, on the other hand, both cholinergics and secretin easily stimulate pepsin secretion from Heidenhain pouches.[6]

The results show, in agreement with Venables,[9,10] that after vagotomy the sensitivity of both chief and parietal

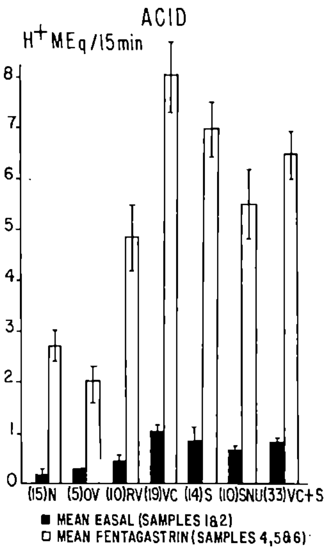

FIG. 3. HCl secretion per 15 min. before and after pentagastrin (males only). Basal bars are means of two resting collections (2 and 3) expressed as secretion per 15 min. ± SE. Pentagastrin bars are the means ± SE expressed as secretion per 15 min. calculated from the first three post-pentagastrin samples (4, 5 and 6). C, controls; OV, old vagotomies; RV, recent vagotomies; VC, visible craters; S, duodenal scarring; SNU, symptoms but no ulcer. Numbers in parenthesis = number of subjects.

TABLE 1. *The Relationship Between Pepsin Secretion and Pentagastrin in Dogs*

Dose Pentagastrin μg/min Intravenously	0	0.5	1.0	2.0	4.0
	Pepsin units/10 min.				
Before Vagotomy	52.0 ± 21	154.0 ± 39	183.0 ± 53	218.0 ± 88	214.0 ± 68
After Vagotomy	7.6 ± 2.1	43.3 ± 3.3	72.0 ± 9.8	116.9 ± 27	97.5 ± 20

cells to pentagastrin was reduced but it seems more slowly in the former than in the latter. Unlike Venables we found a greater difference between pre- and post-vagotomy acid than pepsin in both recent and old vagotomies. In ten men Cowley[2] has found a similar reduction in the acid and pepsin response to a cholinergic stimulant. Two months after vagotomy acid, but not pepsin, was significantly lower than the pre-vagotomy response.

There is nothing in the results to suggest that estimation of pepsin adds to the value of gastric analysis in the diagnosis of peptic ulcer or that it aids in prognosis. Figs. 2 and 3 suggest that a high post-pentagastrin pepsin is concomitant with symutoms of dyspesia whether an active ulcer is present or not but that the highest acids are seen in those with visible ulcer craters.

It is clear that the vagotomized dog and human stomachs are alike with respect to the pepsin response to pentagastrin and that results from Heidenhain pouches in dogs cannot be used to predict the behavior of the vagotomized stomach in either species.

Summary

Pentagastrin, 6.0 μg/kg subcutaneously significantly increases pepsin secretion in asymptomatic unoperated controls and in patients following either recent or old vagotomy. In recent vagotomy patients both stimulated and unstimulated acid and pepsin were significantly higher than in controls or old vagotomies. The acid in the recent vagotomies was significantly lower, both stimulated and unstimulated, than in patients with ulcer craters or scarring whether these were considered as two groups or one. Basal pepsins in the recent vagotomies were not different from any of those in the three unoperated symptomatic groups. Stimulated pepsins in the recent vagotomies were marginally less than in the visible crater group. They were not less than the other two symptomatic groups either treated separately or amalgamated with the visible crater patients.

Pentagastrin increased pepsin secretion in vagotomized dogs. The Heidenhain pouch does not mirror the behavior of pepsin in the intact or vagotomized stomach.

Acknowledgments

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References

1. Anson, M. L.: The Estimation of Pepsin, Trypsin, Papain, and Cathepsin with Hemoglobin. J. Gen. Physiol., **22**:79, 1938.
2. Cowley, D. J.: Effect of Truncal Vagotomy on Acid and Pepsin: Response to a Cholinergic Drug in Man. Gut, **13**:99, 1972.
3. Dutt, B. and Magee, D. F.: Pepsin Secretion by Heidenhain Pouches in Dogs. Am. J. Physiol., **223**:480, 1972.
4. Emas, S. and Grossman, M. I.: Effect of Truncal Vagotomy on Acid and Pepsin Response to Histamine and Gastrin in Dogs. Am. J. Physiol., **212**:1007, 1967.
5. Hollander, F.: Laboratory Procedures in the Study of Vagotomy (With Particular Reference to the Insulin Test). Gastroenterology, **11**:419, 1948.
6. Nakajima, S., Nakamura, M. and Magee, D. F.: Effect of Secretin on Gastric Acid and Pepsin Secretion in Response to Various Stimuli. Am. J. Physiol., **216**:87, 1969.
7. Robertson, C. R., Langlois, K., Martin, C. G., Slezak, G. and Grossman, M. I.: Release of Gastrin in Response to Bathing the Pyloric Mucosa with Acetylcholine. Am. J. Physiol., **163**:27, 1950.
8. Schofield, B.: The Inhibition of Pepsin Output in Separated Gastric Pouches in Dogs Following Feeding and its Correlation with Motility Changes. Gastroenterology, **37**:169, 1959.
9. Venables, C. W.: Effect of Vagotomy upon Pepsin Secretion in Man and its Possible Role in Duodenal Ulcer (abstract). Gut, **12**:865, 1971.
10. Venables, C. W.: The Value of a Combined Pentagastrin/Insulin Test in Studies of Stomach Ulceration. Brit. J. Surg., **57**:757, 1970.

Experimental Study of Hyperdynamic vs. Stagnant Mesenteric Blood Flow in Portal Hypertension

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SOON AFTER McINDOE[23] AND LATER WHIPPLE[38] proposed that portal hypertension in patients with hepatic cirrhosis was caused by obstruction to the flow of portal blood, extensive clinical and pathologic data emerged to support this viewpoint.[14,18,28] The portal circulation, analogous to the systemic circulation in congestive heart failure, was envisioned as "passively congested" and the enlarged spleen of Banti's syndrome as the end result of "backward" transmission of portal pressure.[30] Despite wide acceptance of this theory, several inconsistencies have not been resolved.

In experimental animals, chronic restriction to portal blood flow produces neither significant portal hypertension nor bleeding esophageal varices and ascites,[9,32,36] typical features of human hepatic cirrhosis. Furthermore, the hemodynamic abnormalities in portal hypertension from cirrhosis are in distinct contrast to the stagnant circulation of congestive heart failure. In heart failure, the "pump" fails, blood flow slows[31] and arteriovenous oxygen extraction widens.[13] Accordingly, oxygen saturation in vena caval or pulmonary arterial blood is decreased, fulfilling the criteria of what Barcroft aptly termed "stagnant anoxia."[2] On the other hand, while transit times in the portal vein proper may be considerably delayed in patients with hepatic cirrhosis,[16,24] portal blood is highly oxygenated[42,46] suggesting that splanchnic blood flow is not reduced. Furthermore, bounding peripheral pulses, cardiomegaly, elevated cardiac output and lowered systemic vascular resistance are common features.[21,25] Accordingly, the existence of multiple splanchnic arteriovenous fistulae has been postulated as an alternative mechanism of portal hypertension.[17]

Investigations into the dynamics of the blood and lymph circulations in patients with hepatic cirrhosis suggest that increased vascular resistance to portal flow operates in concert with increased splanchnic blood flow to produce portal hypertension and its sequelae.[43] Whereas raised resistance to portal flow through the cirrhotic liver may reduce flow in the portal vein itself,[24] mesenteric and splenic arterial flow may nonetheless be maintained or actually increased.[20] As the mesenteric circulation comprises two-thirds to three-fourths of portal blood flow,[15] the response of this major circulation as well as of the thoracic duct lymph circulation was studied in dogs under conditions which reproduced an exclusively stagnant circulation, a hyperdynamic circulation or a combination of both. The experimental data in these three different situations were then compared to findings in patients with hepatic cirrhosis.

Materials and Methods

Eighteen fasted dogs (wt. 16–27 kg) were anesthetized lightly with pentobarbital sodium (25 mg/kg) and respiration controlled at constant rate and volume with a Harvard Piston respirator using room air. Small supplemental doses of pentobarbital (50 mg) were periodically administered to maintain a constant level of anesthesia. Intraperitoneal temperature was maintained between 36–38° C. using externally applied hot water plastic bottles. The aorta, superior mesenteric vein, and right atrium were cannulated via the femoral artery, a jejunal vein and femoral vein respectively and arterial and venous pressure continuously recorded on a multi-

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channel direct writing polygraph (Hewlett-Packard). Arterial and mesenteric venous blood samples were aspirated serially and blood pH PO_2, and PCO_2 determined using an Instrumentation Laboratory gas analyzer. Oxygen saturation was calculated from a Severinghaus nomogram based on partial pressure of oxygen, pH and temperature. Hemoglobin concentration was serially determined on these same samples of blood (cyanomethemoglobin method) and oxygen content computed by multiplying the saturated hemoglobin (HbO_2) by 1.34 ml O_2/gm HbO_2. A non-cannulating square-wave electromagnetic flow probe was placed on the superior mesenteric artery and blood flow continuously followed on a Carolina Electronics recorder. Mesenteric oxygen consumption (ml O_2/min) was determined by multiplying the superior mesenteric arterial (SMA) flow (liters/min) by the difference (arterial-mesenteric venous) in oxygen content (ml O_2/liter). Mesenteric vascular resistance (peripheral resistance units) was calculated as the quotient of the arterial-mesenteric venous pressure (mm Hg)/SMA flow (ml/min).

The thoracic duct was cannulated in the left neck with polyethylene tubing for determination of flow rate (gravity drainage) and protein content of thoracic duct lymph was measured (refractometry) and expressed as a ratio to the protein content of blood sera. A micrometer was placed about the portal vein for controlled constriction. After control values were obtained for thirty minutes, the experimental maneuvers were accomplished with no further direct manipulation. Experimental animals were divided into three groups.

Group I (Eight Dogs)

A. In three dogs, the portal vein was constricted acutely to a portal pressure of 25–30 mm Hg and superior mesenteric arterial flow, arterial and mesenteric venous PO_2, blood hemoglobin concentration, flow rate of thoracic duct lymph and protein content of thoracic duct lymph and serum serially determined. From these values, blood oxygen saturation and oxygen content, mesenteric oxygen consumption, and mesenteric vascular resistance were calculated.

B. In five other dogs, the portal vein was constricted in increments of 5 mm Hg to a mesenteric venous pressure of 30 mm Hg and at each level of portal pressure, the same measurements and calculations were carried out as in A.

Group II (Five Dogs)

Glucagon (Lilly), in 30 cc of saline, was infused into the right atrium at a rate of 0.5 ml/min via a Harvard Infusion Pump for a total of 60 minutes (total dose 30 μg/kg) and measurements and calculations serially carried out as in Group I.

Group III (Five Dogs)

The portal vein was partially constricted to raise mesenteric venous pressure 50%. After thirty minutes, glucagon was infused as in Group II and similar determinations made.

Results

Group I

A. Acute constriction of the portal vein to a portal pressure of 25–30 mm Hg produced an immediate fall in superior mesenteric arterial flow and a rise in mesenteric vascular resistance (Fig. 1). There was a progressive decrease in mesenteric venous blood oxygen saturation and pH (7.35 ± 0.01 to 7.30 ±0.03) and a corresponding increase in oxygen extraction by the gut (Fig. 1). This maneuver also led to a marked increase in thoracic duct lymph flow and a pronounced fall in the lymph to serum protein ratio (Fig. 1).

B. Stepwise constriction of the portal vein at increments of 5 mm Hg in portal pressure to 30 mm Hg produced a progressive fall in superior mesenteric arterial flow and a rise in mesenteric vascular resistance (Fig. 2). Mesenteric venous blood oxygen saturation decreased progressively as did pH (86.4 ± 1.4 to 57.9 ± 7.7% and 7.41 ± 0.02 to 7.37 ± 0.02 respectively). Oxygen extraction (arterial-mesenteric venous oxygen content) rose sharply, thereby maintaining mesenteric oxygen consumption (Fig. 2). Thoracic duct lymph flow increased markedly while lymph-to-serum protein ratio fell gradually (Table 1). Arterial pressure declined as portal pressure exceeded 20 mm Hg.

Group II

Despite doubling superior mesenteric arterial flow after infusion of glucagon, portal venous pressure rose very little. Mesenteric venous blood oxygen saturation increased slightly as oxygen extraction across the gut narrowed. Thoracic duct lymph flow increased moderately while lymph-to-serum protein ratio decreased (Fig. 3). A modest fall in mean arterial pressure associated with tachycardia was also observed.

Group III

Slight constriction of the portal vein combined with infusion of glucagon markedly raised portal pressure (23–28 mm Hg), approximately to the level reached in Group I. Unlike Group I, superior mesenteric arterial flow was increased and vascular resistance to mesenteric flow lowered. Mesenteric venous blood remained highly saturated with oxygen and oxygen extraction across the gut did not change significantly. Thoracic duct lymph flow greatly increased as lymph-to-serum protein ratio

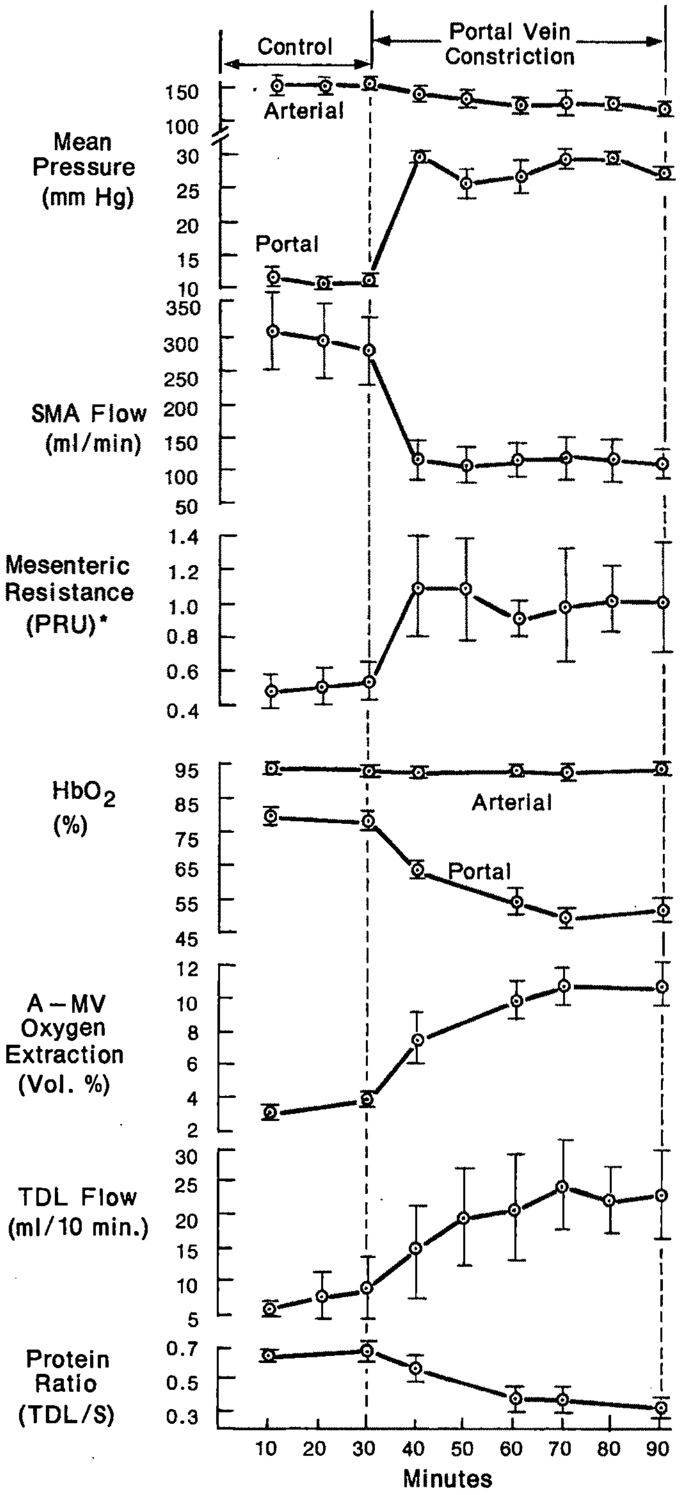

FIG. 1. Circulatory dynamics in the extrahepatic portal bed after induction of portal hypertension by narrowing of the portal vein. Note the pronounced fall in superior mesenteric arterial (SMA) flow and rise in mesenteric vascular resistance accompanied by progressive decline in oxygen saturation (HbO_2) of mesenteric venous blood and widened arterial-mesenteric venous (A-MV) oxygen extraction. Thoracic duct lymph (TDL) flow also increased whereas thoracic duct lymph/serum (TDL/S) protein decrease. These findings represent "stasis" or "passive congestion" of the portal system.

* PRU = peripheral resistance units (arterial-portal venous pressure) (mm Hg)/SMA flow (ml/min)

fell markedly. Mean arterial pressure decreased slightly after administration of glucagon (Fig. 4).

Discussion

In dogs, *acute* portal vein obstruction produces marked portal hypertension accompanied by increased mesenteric vascular resistance, decreased mesenteric arterial inflow and increased production of extrahepatic portal lymph. Mesenteric venous blood oxygen content undergoes marked desaturation which temporarily maintains extrahepatic splanchnic oxygen consumption. In this situation, the portal circulation of blood is truly stagnant and passive congestion is an appropriate designation. On the other hand, chronic portal vein obstruction does not produce sustained portal hypertension.[9,32,36]

When glucagon, a hormone secreted by α islet cells of the pancreas, is administered to dogs in pharmacologic doses, cardiac output, mesenteric arterial and portal venous flow increase dramatically.[19,22] Mesenteric venous blood remains highly oxygenated and thoracic duct lymph flow rises. Despite a markedly hyperdynamic circuit, however, portal pressure elevation and mesenteric congestion is minimal.

In contrast to isolated increases in either portal vascular resistance or splanchnic blood flow, combined increases in both resistance and flow closely simulate the characteristic circulatory pattern in patients with hepatic cirrhosis.[11,12,41] Thus, when infusion of glucagon is combined with portal vein constriction, marked portal hypertension (25 mm Hg) results with highly oxygenated mesenteric venous blood (85% saturation) and greatly increased formation of thoracic duct lymph low in protein content derived from the preportal splanchnic bed.

The "backward" theory of portal "stasis" (increased portal vascular resistance) in cirrhosis is supported by abundant clinical and pathologic evidence of decreased hepatic sinusoidal and venular drainage capacity.[14,18,28] Nonetheless, in dogs neither acute restriction (which leads to reduced mesenteric venous oxygen saturation) nor chronic restriction of portal flow (which fails to elevate portal pressure) produce the essential hemodynamic features of patients with cirrhosis.

In contrast, the "forward" theory postulates as the primary mechanism of portal hypertension increased portal flow from arteriovenous fistulae in the digestive tract and spleen.[17,29,45] Traumatic splenic and mesenteric arterio-portal fistulae,[34,35] congenital splenic arteriovenous malformation [1,7,26,27,37] and myeloproliferative disorders associated with massive splenomegaly[4,33] are occasional sources of increased portal flow and portal hypertension. Treatment of these conditions by closure of the fistulae, obliteration of the malformation or splenectomy controls the hyperdynamic circuit and thereby relieves varix hemorrhage, ascites and hypersplen-

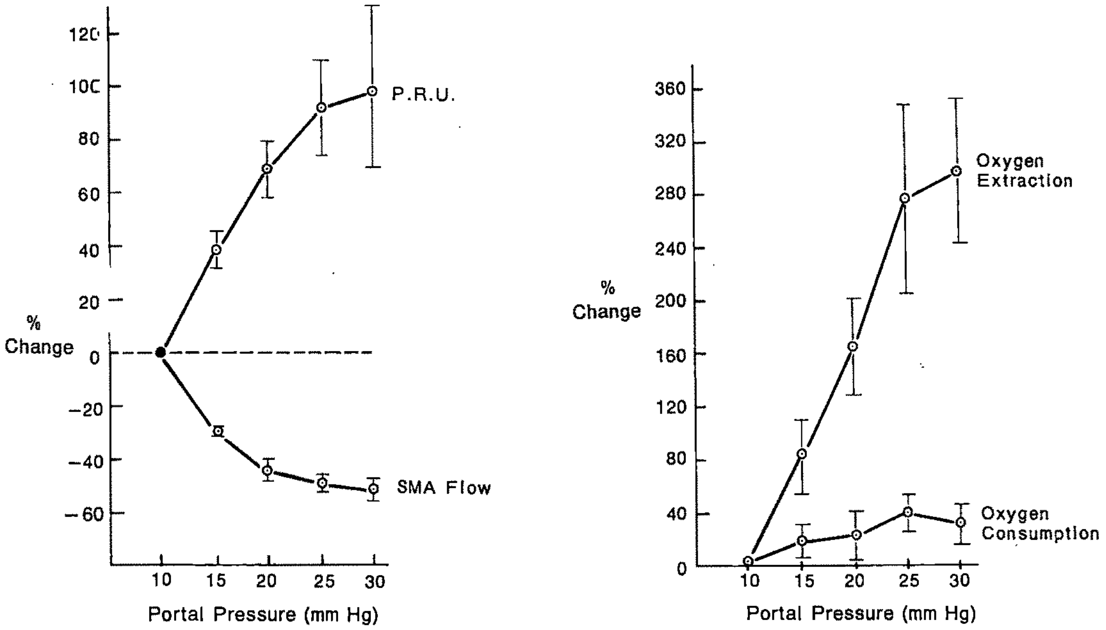

FIG. 2. Effect of progressively narrowing the portal vein in the dog. As portal pressure rises, there is a gradual reduction in superior mesenteric arterial (SMA) flow and a marked rise in mesenteric vascular resistance (PRU) (left). As blood flow slows, oxygen extraction (arterial-mesenteric venous oxygen content) widens and thereby maintains splanchnic oxidative metabolism (oxygen extraction × SMA flow) (right). These findings represent "stasis" or "passive congestion" of the portal system.

ism.[1,4,7,26,27,34,35,37] In patients with hepatic cirrhosis, high cardiac output,[21,25] low systemic peripheral vascular resistance[21,25] and highly oxygenated portal venous blood[33,45] support the concept of a hyperdynamic rather than stagnant portal circulation. In fact, enlarged splanchnic arteries[6,46] particularly to the spleen[10,39] are not uncommonly observed. Moreover, splenectomy or splenic artery ligation[5,10,40,43] is occasionally all that is necessary for portal decompression. Nonetheless, in experimental animals, hyperdynamic flow alone as produced by glucagon infusion fails to raise portal pressure significantly.

The similarity between the circulatory dynamics of human cirrhosis and that following experimental glucagon infusion *combined* with portal vein constriction suggests that their cause, too, may be similar; that is, increased portal vascular resistance combined with increased splanchnic arterial inflow. In the patient with cirrhosis, this derangement could stem from failure (autoregulatory escape) of splanchnic arteriolar vasoconstrictor response to rising intrahepatic resistance to portal flow. It is known that patients with hepatic cirrhosis fail to exhibit pulminary arteriolar vasoconstrictor response during hypoxic stimulation.[8] In addition, a generalized disturbance in vasomotor control is suggested by the frequent observation of lowered systemic vascular resistance and high cardiac output.

TABLE 1. *Acute Changes in Thoracic Duct Lymph (TDL) Flow and Protein Content of Thoracic Duct Lymph/Serum (TDL/S) Ratio with Increasing Portal Pressure Level After Progressive Constriction of the Portal Vein*

Portal Pressure (mm Hg)	TDL Flow (μg/min/kg)	TDL/S Protein Content
10	19.0 ± 2.5	0.74 ± 0.04
15	22.0 ± 4.0	0.72 ± 0.04
20	25.2 ± 3.6	0.66 ± 0.03
25	40.6 ± 7.1	0.50 ± 0.04
30	62.2 ± 12.1	0.31 ± 0.05

In the present study, the stepwise increase in portal pressure was produced by fixed and arbitrary combinations of increased portal vascular resistance and splanchnic inflow. Nonetheless, neither increased vascular resistance (portal stasis) nor increased blood flow alone (splanchnic-arteriovenous fistulae) are likely to produce portal hyptertension in man. Instead, both abnormalities in combination (increased splanchnic inflow and increased portal vascular resistance) seem necessary to generate and sustain portal hypertension in association with highly oxygenated portal blood. Other clinical data conform to this viewpoint. Thus, under conditions where mesenteric arterial flow is limited, increased resistance to portal flow is offset and portal pressure elevation minimized. For example, in patients with portal hypertension, infusion of vasopressin into the superior mesenteric artery reduces portal pressure and thereby controls esophageal varix hemorrhage.[3] Similarly in congestive heart failure, despite severe resistance to transhepatic portal flow posed by central venous hypertension and intense hepatic congestion, portal hypertension rarely develops as splanchnic blood flow is reduced in this condition. Accordingly, in heart failure varix hemorrhage and ascitic fluid low in protein arising from the gut is the exception whereas ascitic fluid high in protein arising from the congested liver is the rule.[44]

The divergent circulatory patterns already described in patients with portal hypertension also support the concept that portal pressure elevation in man results from a spectrum of disturbances in splanchnic blood flow combined with increased portal vascular resistance. These clinical data taken together with the present experimental data suggest that therapeutic approaches to ascites and varix hemorrhage should likewise differ. Thus, no single operative or non-operative approach to this complex physiologic problem can be uniformly applied. When resistance to portal flow predominates,

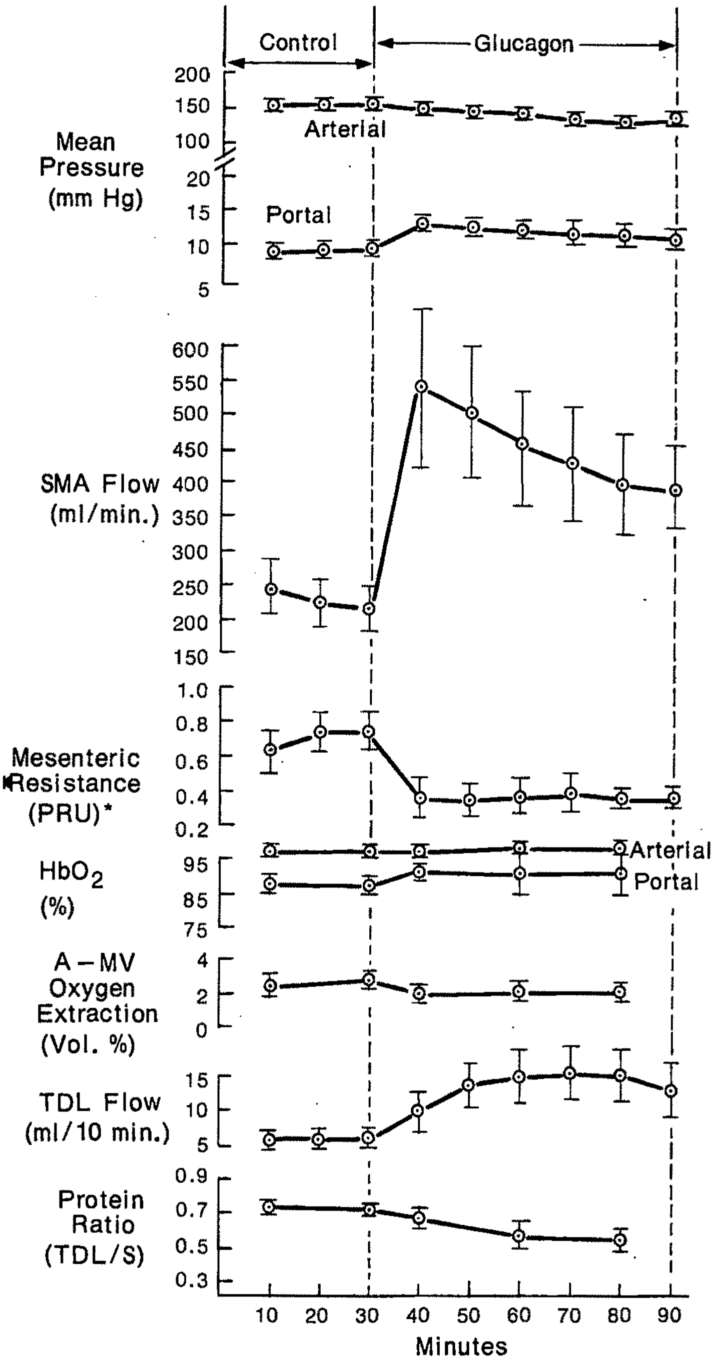

Fig. 3. Circulatory dynamics of extrahepatic portal bed after induction of hyperdynamic mesenteric blood flow by systemic infusion of glucagon. Despite doubling of superior mesenteric arterial (SMA) flow, portal pressure, mesenteric venous oxygen saturation (HbO_2) and arterial-mesenteric venous (A-MV) oxygen extraction were minimally altered. Mesenteric vascular resistance decreased as SMA flow increased. There was also a modest increase in thoracic duct lymph (TDL) formation and a slight fall in thoracic duct lymph/serum (TDL/S) protein ratio.

* PRU = arterial-mesenteric venous pressure (mm Hg)/SMA flow (ml/min).

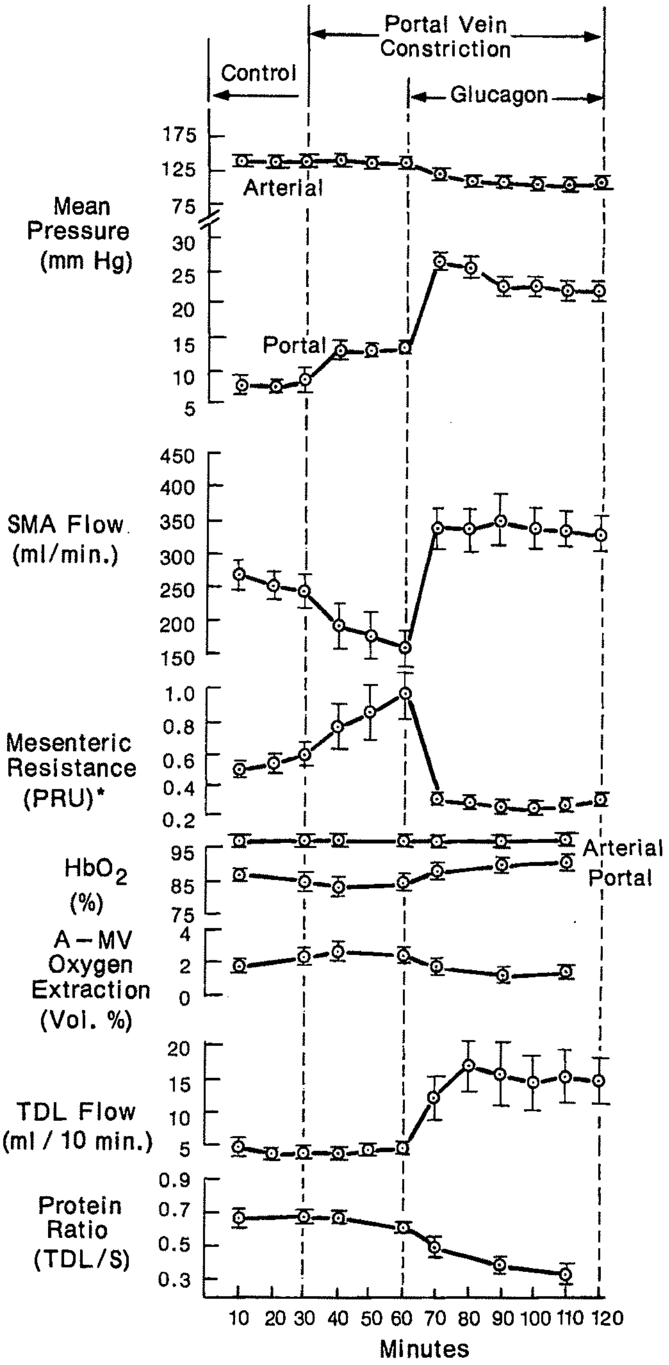

Fig. 4. Circulatory dynamics in the extrahepatic portal bed after induction of portal hypertension by minimal narrowing of portal vein combined with systemic infusion of glucagon. Superior mesenteric arterial (SMA) flow was slightly increased and mesenteric vascular resistance lowered. Mesenteric venous blood oxygen saturation (HbO_2) remained high and arterial-mesenteric venous (A-MV) oxygen extraction unaltered. Thoracic duct lymph (TDL) formation is similarly increased and thoracic duct lymph/serum (TDL/S) protein content reduced. These findings represent "active congestion" in contrast to "passive congestion" (Fig. 1 & 2) of the portal system.

* PRU = arterial-mesenteric venous pressure (mm Hg)/SMA flow (ml/min).

decompression by portasystemic shunt may be appropriate. However, enhancement of mesenteric vasomotor control by infusion of vasopressin into the superior mesenteric artery limits mesenteric flow and thereby provides temporary portal decompression. On the other hand, when increased splanchnic arterial flow predominates with minimally increased portal resistance, then splenectomy or in theory restricting mesenteric inflow by "banding" the superior mesenteric artery or resection of small bowel may also relieve ascites and varix hemorrhage. Reduction in mesenteric blood flow below a critical minimum necessary for intestinal survival is a limiting factor in the latter approach to portal decompression.

In conclusion, these experiments suggest that elevation in portal pressure in man requires a combination of increased resistance to portal flow in conjunction with failure of mesenteric or splenic arterioles to regulate arterial inflow. Although flow in the portal vein proper may be stagnant, total splanchnic blood flow and preportal capillary perfusion need not be diminished and may actually be increased. Highly oxygenated mesenteric venous blood in portal hypertension conforms with this viewpoint. Precapillary splanchnic arteriovenous shunting need not be involved. The term "passive congestion" should be replaced by the more accurate designation of "active congestion" to characterize the circulatory derangement in human portal hypertension.

Summary

To determine the relative importance of hyperdynamic vs. stagnant masenteric blood flow in the pathophysiology of portal hypertension, 18 dogs were studied before and after acute portal vein constriction, infusion of glucagon intravenously and during *combined* portal vein constriction with infusion of glucagon. Arterial and portal pressure, superior mesenteric arterial flow, mesenteric vascular resistance, mesenteric venous oxygen saturation, splanchnic oxygen extraction and consumption, and thoracic duct lymph flow and protein content were serially monitored.

Although acute portal vein constriction produced marked portal hypertension and increased flow of thoracic duct lymph low in protein content, this maneuver was associated with a pronounced reduction in mesenteric arterial flow and mesenteric venous blood oxygen saturation and with a sharp rise in mesenteric vascular resistance and splanchnic oxygen extraction ("passive congestion"). In contrast, infusion of glucagon doubled mesenteric arterial flow with maintenance of high oxygen saturation of mesenteric venous blood, low mesenteric vascular resistance and a modest increase in flow of thoracic duct lymph, slightly lowered in protein content. Portal pressure, however, was minimally increased. On the other hand, slight portal vein constriction combined with infusion of glucagon produced marked portal hypertension with highly oxygenated mesenteric venous blood and greatly increased flow of thoracic duct lymph low in protein content. Mesenteric arterial flow was slightly increased, and mesenteric vascular resistance slightly lowered ("active congestion").

When compared to findings in patients with hepatic cirrhosis and portal hypertension, these data suggest that increased portal vascular resistance operates in concert with increased splanchnic blood flow to produce the divergent clinical patterns of portal hypertension. "Active congestion" rather than "passive congestion" more accurately characterizes the circulatory derangement of human portal hypertension.

References

1. Adams, H. D.: Congenital Arteriovenous and Cirsoid Aneurysm. Surg. Gynecol. Obst., **92**:693, 1957.
2. Barcroft, J.: Physiological Effects of Insufficient Oxygen Supply. Nature, **106**:125, 1920–21.
3. Baum, S. W. and Nusbaum, M.: The Control of Gastrointestinal Hemorrhage by Selective Mesenteric Arterial Infusion of Vasopressin. Rad., 98:497, 1961.
4. Berman, I. R., Stahl, W. M., Dumont, A. E. and Berenbaum, E. R.: Hemodynamics of High Inflow Portal Hypertension and Report of a Case. Ann. Surg., **167**:265, 1968.
5. Blain, A. W. and Blain, A. W.: Ligation of the Splenic Artery, The Operation of Choice in Selected Cases of Portal Hypertension and Banti's Disease Syndrome. Ann. Surg., **131**:92, 1950.
6. Boijsen, E.: Selective Angiography of the Celiac Axis and Superior Mesenteric Artery in Cirrhosis of the Liver. Rev. Int. Hepat., **15**:323, 1965.
7. Bucholz, A. A.: Arteriovenous Fistula of the Splenic Vessels. Ann. Surg., **149**:590, 1959.
8. Daoud, F. S., Reeves, J. T. and Schaefer, J. W.: Failure of Hypoxic Pulmonary Vasoconstriction in Patients with Liver Cirrhosis. J. Clin. Invest., **51**: 1076, 1972.
9. Douglas, T. C., Mehn, W. H., Lounsberg, B., Swigert, L. L. and Tanturi, C. A.: Attempts at Experimental Production of Portal Hypertension. Arch. Surg., **62**:785, 1951.
10. Dumont, A. E., Berman, I. R., Stahl, W. M. and Ring, S. M.: Significance of an Enlarged Splenic Artery in Patients with Bleeding Varices. Ann. Surg., **175**:466, 1972.
11. Dumont, A. E. and Mulholland, J. H.: Flow Rate and Composition of Thoracic Duct Lymph in Patients with Cirrhosis. N. Engl. J. Med., **263**:471, 1960.
12. Dumont, A. E. and Witte, M. H.: Contrasting Patterns of Thoracic Duct Lymph Formation in Hepatic Cirrhosis. Surg. Gynecol. Obstet., **122**:524, 1966.
13. Filley, G. F.: Oxygenation and the Arterial PO_2. *In* Acid-Base and Blood Gas Regulation. Phila., Lea and Febiger, 75, 1971.
14. Friedman, E. W. and Weiner, R. S.: Estimation of Hepatic Sinusoid Pressure by Venous Catheters and Estimation of Portal Pressure by Hepatic Vein Catherization. Amer. J. Physiol., **165**:527, 1951.
15. Grim, E.: The Flow of Blood in the Mesenteric Vessels *In* Handbook of Physiology. Circulation 2, Vol. 2. W. P. Hamilton, editor. Washington, D. C., Physiologic Soc., 1439, 1963.
16. Hunt, A. H.: In Investigation of the Pressures and Speeds in the Portal Circulation. IV Congress de Gastroenterologie, Paris Masson, June, 1954.

17. Johnson, G., Dart, C. H., Peters, R. M. and MacFie, J. A.: Hemodynamic Changes with Cirrhosis of the Liver: Control of Arteriovenous Shunts During Operation for Esophageal Varices. Ann. Surg., **163**:692, 1966.

18. Kelty, R. H., Baggenstoss, A. H. and Butt, H. R.: The Relation of the Regenerated Liver Nodule to the Vascular Bed in Cirrhosis. Gastroenterology, **15**:285, 1950.

19. Kock, N. G., Tibblin, S. and Schenk, W. G.: Mesenteric Blood Flow Responses to Glucagon Administration. Arch. Surg., **100**:280, 1970.

20. Kotelanski, B., Groszmann, N. R. and Cohn, J. N.: Circulation Times in the Splanchnic and Hepatic Beds in Alcoholic Liver Disease. Gastroenterology, **63**:102, 1972.

21. Kowalski, H. J. and Adelmann, W. H.: The Cardiac Output at Rest and in Laennec's Cirrhosis. J. Clin. Invest., **32**: 1025, 1953.

22. Madden, J. J., Ludewig, R. N. and Wangensteen, S. L.: Effects of Glucagon on the Splanchnic and the Systemic Circulation. Amer. J. Surg., **122**:85, 1971.

23. McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis. Arch. Path., **5**: 23, 1928.

24. Moreno, A. H., Burchell, A. R., Russelot, L. M., *et al.*: Portal Blood Flow in Cirrhosis of the Liver. J. Clin. Invest., **46**:436, 1967.

25. Murray, J. F., Dawson, A. M. and Sherlock, S.: Circulatory Changes in Chronic Liver Disease. Amer. J. Med., **24**: 358, 1958.

26. Nissan, S. and Bar-Maor, J. A.: Bleeding Esophageal Varices Due to Splenic Arteriovenous Fistulae. Amer. J. Gastro., **55**:379, 1971.

27. Owens, J. C. and Caffey, R. J.: Aneurysm of Splenic Artery Including a Report of Six Additional Cases. Int. Arch. Surg **97**:313, 1953.

28. Popper, H., Elias, H. and Petty, D. E.: Vascular Pattern of the Cirrhotic Liver. Amer. J. Clin. Path., **22**:717, 1952.

29. Ravenna, P.: Banti Syndrome (Fibrocongestive Splenomegaly): Definition, Classification and Pathogenesis. Arch. Int. Med., **66**:879, 1940.

30. Rousselot, L. M.: Congestive Splenomegaly (Banti's Syndrome). Bull. N. Y. Acad. Med., **15**:188, 1939.

31. Sarnoff, S. J.: Myocardial Contractility as Described by Ventricular Function Curves. Physiol. Rev., **35**:107, 1955.

32. Schilling, J. A., McCord, A. B., Clausen, S. W., et al: Experimental Ascites. Studies of Electrolyte Balance in Dogs with Partial and Complete Occlusion of the Portal Vein and of the Vena Cava Above and Below the Liver. J. Clin. Invest., 31:702, 1952.

33. Smythe, C. M., Fitzpatrick, H. F. and Blakemore, A. H.: Studies on Portal Venous Oxygen Content in Unanesthetized Man. J. Clin. Invest., **30**:674, 1951.

34. Stone, H. H., Jordan, W. D., Acker, J. J. and Martin, J. D.: Portal Arteriovenous Fistulae. Amer. J. Surg., **109**:191, 1965.

35. Van Way, C. W., Crane, J. M., Riddell, D. H., Foster, J. H.: Arteriovenous Fistulae in the Portal Circulation. Surgery, **70**:876, 1971.

36. Volwiler, W., Grindley, J. H. and Bollman, J. L.: The Relation of Portal Vein Pressure to the Formation of Ascites; an Experimental Study. Gastroenterology, **14**:40, 1950.

37. Von Hellens, A.: Arteriovenous Fistulae as the Cause of Portal Hypertension. Ann. Chir. Gynaecol. Fenn., **49**:410, 1960.

38. Whipple, A. O.: Problem of Portal Hypertension in Relation to Hepatosplenopathies. Ann. Surg., **122**:449, 1945.

39. Williams, R., Condon, R. E., Williams, H. S., *et al.*: Splenic Blood Flow in Cirrhosis and Portal Hypertension. Clin. Sci., **34**:441, 1968.

40. Witte, M. H., Witte, C. L., Cole, W. R. and Koehler, P. R.: Contrasting Patterns of Ascites Formation in Hepatic Cirrhosis. JAMA, **208**:1661, 1969.

41. Witte, M. H., Dumont, A. E., Cole, W. R., *et al.*: Lymph Circulation in Hepatic Cirrhosis: Effect of Portacaval Shunt. Ann. Int. Med., **70**:303, 1969.

42. Witte, C. L., Cole, W. R., Clauss, R. H. and Dumont, A. E.: Splanchnic Tissue Oxygenation: Estimation by Thoracic Duct. Lymph PO_2. Lymphology, **1**:109, 1968.

43. Witte, C. L., Witte, M. H. and Krone, C. L.: Contrasting Hemodynamic Patterns of Portal Hypertension. Ann. Surg., **176**:68, 1972.

44. Witte, C. L., Witte, M. H., Dumont, A. E., *et al.*: Protein Content in Lymph and Edema Fluids in Congestive Heart Failure. Circulation, **40**:623, 1969.

45. Womack, N. A. and Peters, R. M.: The Significance of Splenomegaly in Cirrhosis of the Liver. Ann. Surg., **153**:1006, 1961.

46. Yamauchi, H., Suda, Y., Yanamoto, K., *et al.*: Arteriographic Studies of Splenic and Hepatic Arteries in Portal Hypertension. Tohoku J. Exp. Med., **101**:363, 1970.

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Soft seat can't support vertebrae and low-back muscles
Left leg "frozen" in cramped position
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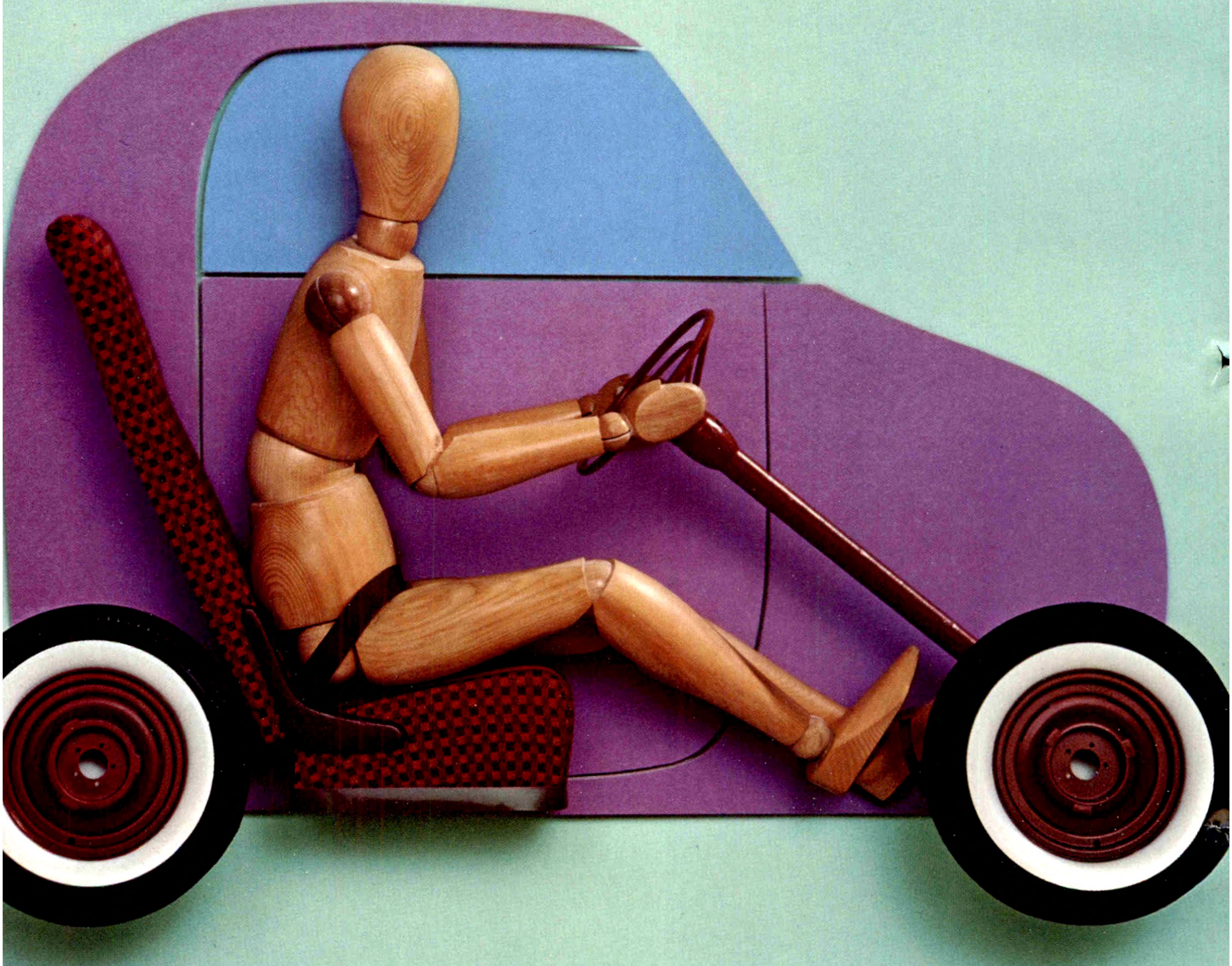

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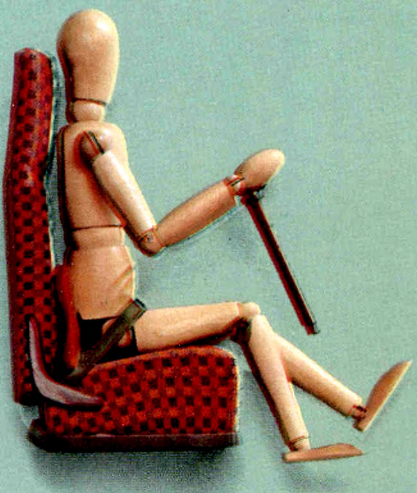

Push front seat forward
strain on back and shou
Insert small cushion bet
back and rear of car seat
can help relieve pain an
Always wear seat belt ar
harness. On long trips g
and stretch every coupl

to treat acute musculoskeletal disorder

ROBAXIN®-750

(methocarbamol)

750 mg. capsule-shaped tablets

the Robaxin® Regimen:

Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort. Have patient insert section of plywood ½-¾″ thick between mattress and box springs. The use of moist heat is often very beneficial.

To relieve the discomforts associated with acute musculoskeletal disorders, Robaxin®-750 is often indicated.* It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

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Indications

Based on a review of this dr
National Academy of Science
Research Council and/or oth
FDA has classified the indicati
"Possibly" effective: Relief c
associated with acute muscul
disorders.
Final classification of the le
indications requires further ir

Contraindications:
Methocarbamol is contraindicat
hypersensitive to any of the ingr

Warnings:
Safe use of Robaxin has not bee
regard to possible adverse effect
development. Therefore, Robax
used in women who are or may
and particularly during early pre
the judgment of the physician th
outweigh the possible hazards.

Adverse Reactions:
Light-headedness, dizziness, drc
allergic manifestations such as u
rash, conjunctivitis with nasal co
vision, headache, fever.

Dosage and Administration
NOTE: Because of limited clinic
younger age group, Robaxin is r
for use in patients under 12 yea
in tetanus.

Adults:
Initial dosage, 2 tablets q.i.d. Ma
1 tablet q. 4h. or 2 tablets t.i.d.

Six grams a day are recommenc
48 to 72 hours of treatment. (Fc
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4 grams a day.

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1.6%; in Concentrate as riboflavin-5-phosphate.

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sorethytan laurate; covered by U.S. Patent No. 2,

BRIEF SUMMARY

INDICATIONS: *in emergency feedings*—Surg
sive burns, fractures and other trauma, severe
diseases, comatose states, etc. may provoke a '
uation with profound alterations in the body's
demands and consequent tissue depletion of nut
result, wound healing may be impaired, enzyme
turbed, hematopoietic tissues affected; hypop
and edema may appear; convalescence is thus p
In such patients M.V.I. (administered in intrave
under proper dilution) contributes optimum vita
toward maintaining the body's normal resistance
processes.

DIRECTIONS FOR USE: M.V.I. is ready for imm
when added to intravenous infusion fluids.
For intravenous feeding, one daily dose of 10 cc.
5 cc. of M.V.I. Concentrate added directly to no
500 cc., preferably 1,000 cc., of intravenous dext
or similar infusion solutions...plasma, protein hy
etc.

PRECAUTION: Allergic reaction has been know
following intravenous administration of solutions
thiamine.

CAUTION: Not to be given as a direct undiluted i
injection as it may give rise to dizziness, faintness

THERAPEUTIC NOTE: Intravenous use should
tinued as early as practical in favor of an intran
oral vitamin preparation, if deemed advisable.

HOW SUPPLIED: M.V.I.—10 cc. ampuls, boxes
100.
M.V.I. CONCENTRATE—5 cc. vials, boxes of 2
in 100's only.

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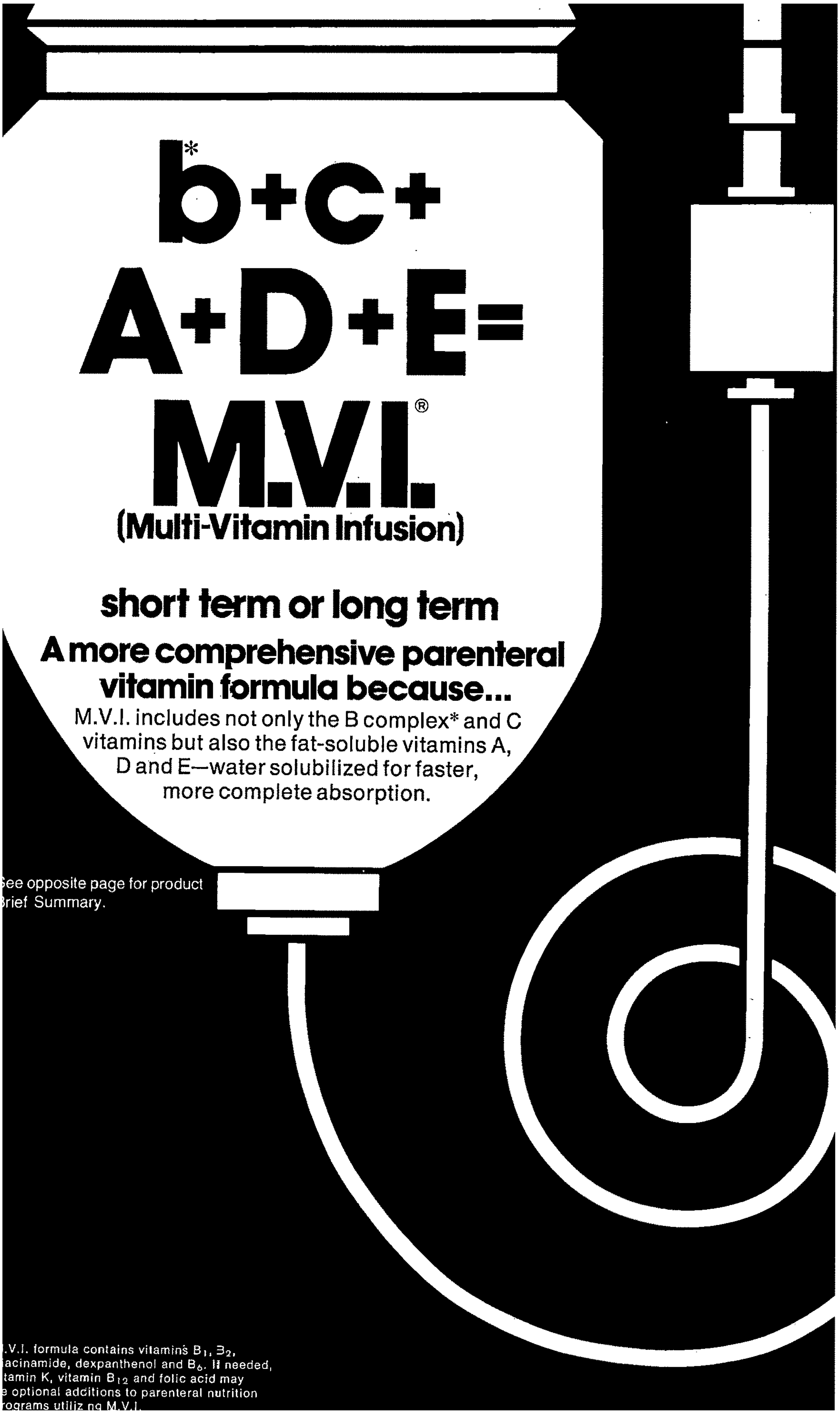

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A more comprehensive parenteral vitamin formula because...

M.V.I. includes not only the B complex* and C vitamins but also the fat-soluble vitamins A, D and E—water solubilized for faster, more complete absorption.

ee opposite page for product
rief Summary.

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acinamide, dexpanthenol and B_6. If needed,
tamin K, vitamin B_{12} and folic acid may
e optional additions to parenteral nutrition
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"I must move thoroughly to be a well-prepped King."
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Dulcolax moves patients the way you want them to

Instead of moving patients to tears . . . like harsh laxatives and traumatic enemas . . . Dulcolax moves them to gentle, predictable relief from post-op constipation. And it yields excellent results in preparing the patient for surgery and/or radiological examination.

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Suppositories: 10 mg.
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**the right move
to replace the enema**

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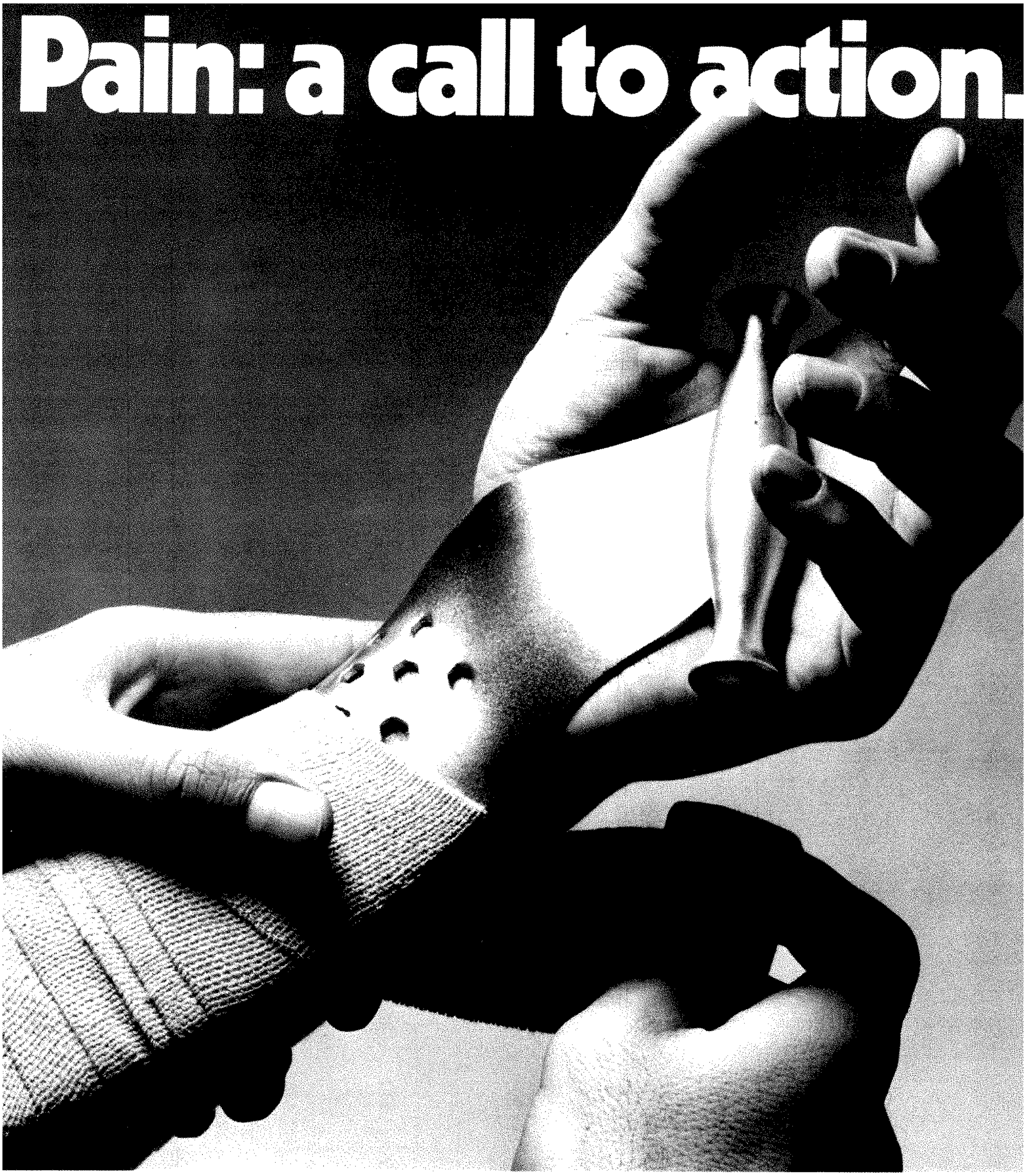
Pain: a call to action.



- ☐ rapid acting
- ☐ effective, reliable oral analgesia in moderate to moderately severe pain
- ☐ oxycodone, the principal ingredient of Percodan, is one of the more readily absorbed oral narcotic analgesics
- ☐ one tablet q.6 h.*

Tablets
Percodan®

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl. (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine. CII

See facing page for Brief Summary

*See dosage and administration section of Brief Summary

EN 6532

Whenever an APC/narcotic is indicated.

Whenever an APC/narcotic is indicated.

Percodan® Tablets CII

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS: *Drug Dependence:* Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Percodan, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, Percodan is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Percodan should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Percodan may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children: Percodan should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Percodan or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: Percodan should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS: The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. The usual adult dose is one tablet every six hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Percodan may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE: *Signs and Symptoms:* Serious overdose with Percodan is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of Percodan may, in addition, result in acute salicylate intoxication.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

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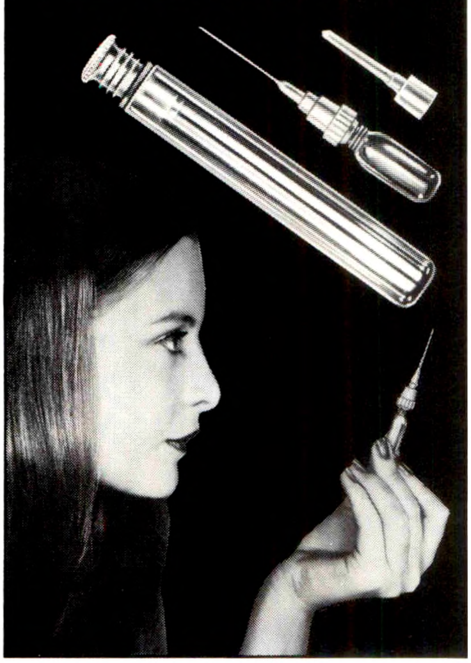

MK-6 gum preparation is a biologically compatible, non-toxic adhesive that bonds live tissue and, in many cases, eliminates the necessity of needle and thread sutures. Extensively tested and proven highly effective in leading Soviet medical institutions, MK-6 works independently or in combination with seams or autoplastic.

MK-6, because it gradually dissolves as the wound heals, saves the time and discomfort of suture removal, as well as avoiding the resultant irritation.

MK-6 is germ-proof and has bactericidal properties that aid in preventing infection. Supplied in a single use applicator in ready-to-use packaging.

For detailed information, write V/O Medexport, 31 Kahovka, Moscow 113461 USSR, Tel. 121-01-54, TELEX 7247. In the U.S., Amtorg Trading Corp., 355 Lexington Avenue, New York, N.Y. 10017.

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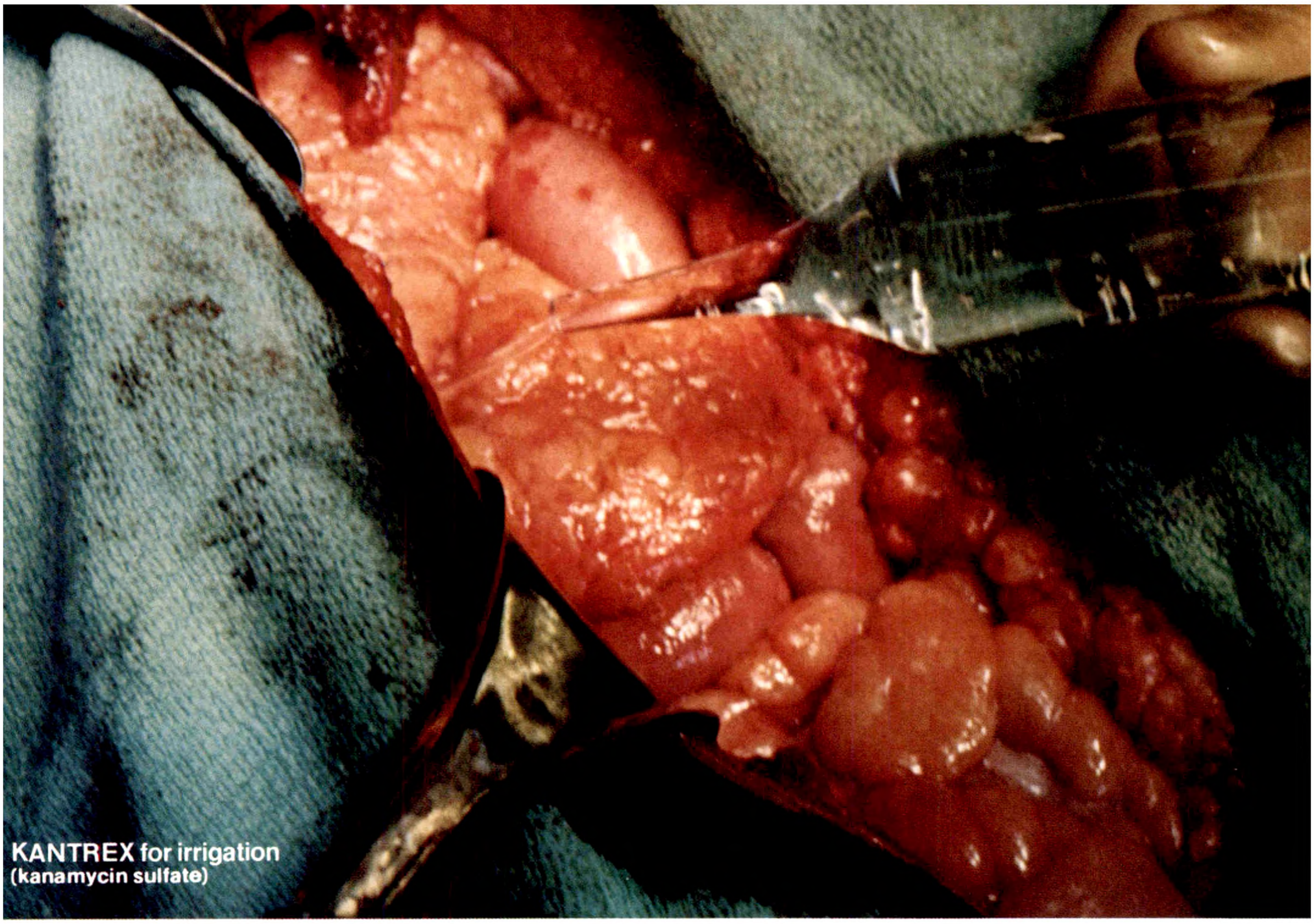
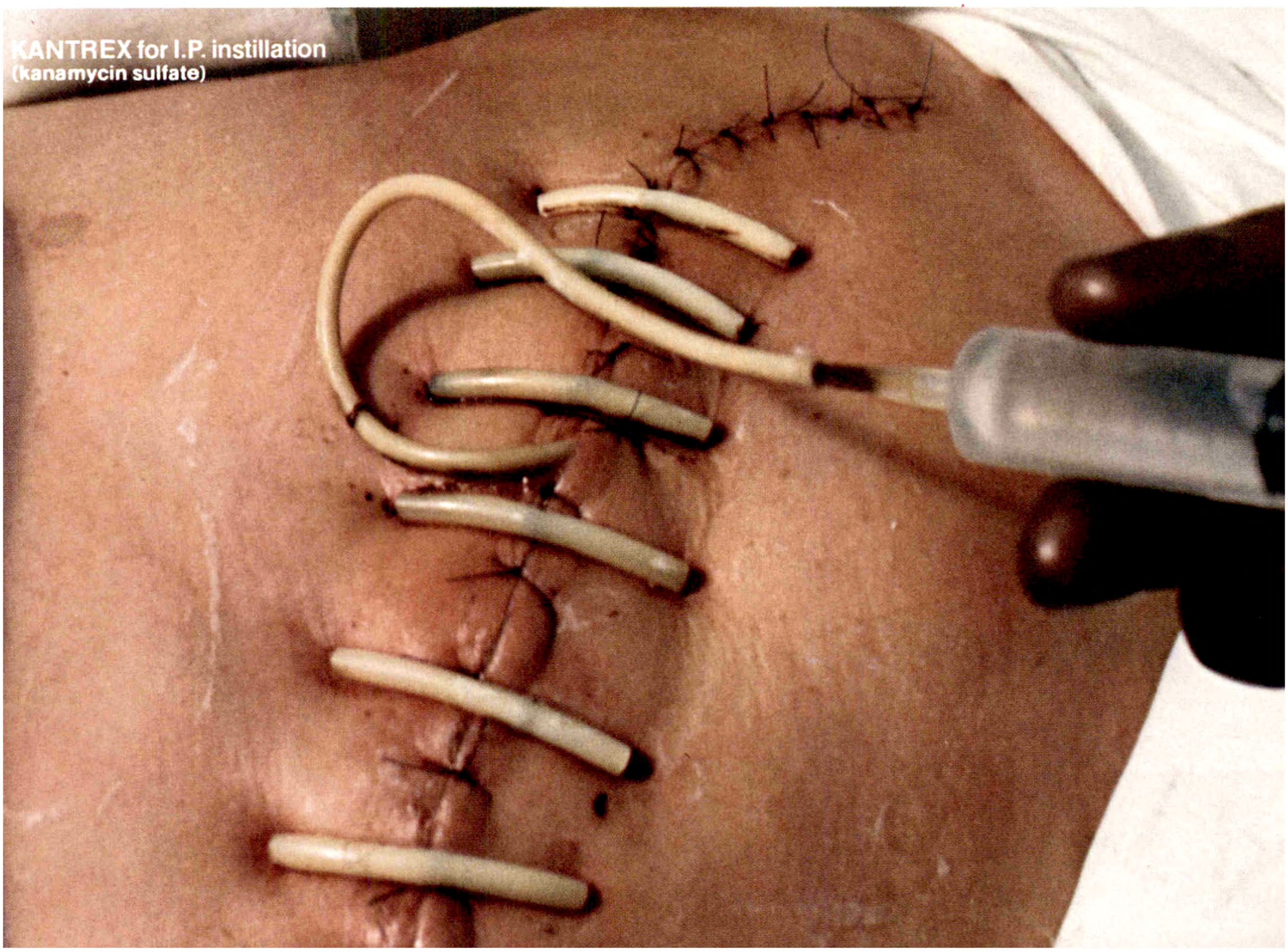

KANTREX for irrigation
(kanamycin sulfate)


KANTREX for I.P. instillation
(kanamycin sulfate)

Before peritoneal contamination leads to peritoneal infection...

Kantrex®
(kanamycin sulfate)
Injection I.M./I.V.

for intraperitoneal use/a surgical adjunct.

Intraperitoneal irrigation during surgery, or instillation post-op, provides immediate contact of Kantrex (kanamycin sulfate injection) with the site of existing or potential infection. Higher local concentrations of the drug can be achieved than with systemic use...without increased risk of toxicity. Absorption with intraperitoneal instillation is about the same as with intramuscular use, while absorption with Kantrex by irrigation is considerably less. High transient peritoneal concentrations have not resulted in any local tissue reactions.

Clinical experience with Kantrex, administered intraperitoneally to a large group of patients suffering from peritoni or peritoneal contamination, indicates that it is effective.[1,2]

Kantrex. A preferred antibiotic with a precise mode of administration for patients with peritoneal soilage or peritoniti

DOSAGE FOR INTRAPERITONEAL USE

KANTREX for irrigation

- Dilute contents of 0.5-Gm. vial in 200 ml. Sterile Water for Injection.
- The resultant 0.25% solution (2.5 mg./ml.) may be used as an irrigant.

KANTREX for I.P. instillation

- Adults: 0.5 Gm. diluted in at least 20 cc sterile distilled water.
- Children: 7.5 mg./Kg. diluted in at least 20 cc. sterile distilled water.
- The above dosages have been repeated every 12 hours for up to 3 days.
- Total daily dosage by all routes should not exceed 1.5 Gm. for adults, or 15 mg./Kg. for children.
- Instill solution through polyethylene tube sutured into wound at closure. If possible, postpone instillation until patient has fully recovered from effects of anesthesia or muscle-relaxing drugs.
- Adjust dosage interval by "creatinine X 9" formula for patients with impaired renal function.*

*e.g.: If serum creatinine is 2 mg./100 ml., multiply by 9; interval between Kantrex doses is 18 hours.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
(10) 6/8/73
For complete information, consult Official Package Circular.

> **Warning:** Irreversible deafness can occur. Tinnitus or vertigo may also occur and indicate vestibular damage and impending deafness. The risk is sharply increased with renal dysfunction. In such cases, decrease size and frequency of doses. Discontinue kanamycin and check hearing if azotemia increases. Watch carefully for ototoxicity in older patients and patients receiving more than 15 Gms. of kanamycin. To avoid neuromuscular paralysis with respiratory depression, postpone intraperitoneal instillation in post-operative patients until recovery from anesthesia and muscle relaxants is complete. Although there have been isolated reports of respiratory depression following intraperitoneal instillation of kanamycin, there is no conclusive proof that this side effect can be produced with recommended doses of the drug. Avoid concurrent use of other ototoxic drugs including ethacrynic acid. Safety in pregnancy is not established.

Indications: Serious infections due to susceptible strains of E. coli, Proteus sp., A. aerogenes, K. pneumoniae, Serratia marcescens and Mima-Herellea. Culture and sensitivity studies should be performed.
Contraindications: A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other agents may be a contraindication if effective, alternative therapy is availabl
Precautions: Obtain audiograms before and during therapy in patients with renal dysfunction when treatment lasts more than 5 days. Stop Kantrex if tinnitus or hearing loss occurs. Hydrate patients to prevent chemical irritation of the renal tubules. Assess renal function periodically, both before and during therapy. If signs of renal irritation occur (casts, cells, proteinuria), increase hydration and reduce the dosage or the frequency of dosage if necessary. In azotemic patients, the frequency (in hours) of doses may be obtained by multiplying the serum creatinine by 9. If azotemia or oliguria occur, discontinue therapy. Mycotic or bacterial superinfection may occur.
Adverse Reactions: Irritation or pain at the injection site, skin rash, drug fever, headache and paresthesias.
Dosage and Administration: The usual dose is 7.5 mg./Kg./12 hours I.M. or I.V. The average adult dose is 1 Gm. daily. The maximum adult total daily dose should not exceed 1.5 Gm. by all routes of administration and the total amount administered should not exceed 15 Gms.

The intravenous route is used only if intramuscular administration is not feasible. The 0.5 Gm. dose is added to 200 ml. of sterile diluent and administered 60-80 drips/minute.

When used as intraperitoneal instillation, the above dose is diluted in 20 ml. of sterile diluent. If possible, instillation should be postponed until after patient is fully recovered from effects of anesthesia and muscle-relaxing drugs.

As aerosol treatment, 250 mg. of Kantrex is diluted with 3 ml. of physiological saline and nebulize.

Kantrex Injection in concentrations of 0.25 percent (2.5 mg./ml.) has been used satisfactorily as an irrigating solution in abscess cavities, pleural spaces, peritoneal and ventricular cavities.
Supplied: Rubber capped vials as a ready-to-use sterile aqueous solution in two concentration 0.5 Gm. in 2 ml., 1.0 Gm. in 3 ml., Pediatric Injection 75 mg. in 2 ml.
References: 1. Cohn, I., Jr., *et al.*: Am. Surg. *29*:756 (Nov.) 1963. 2. Cohn, I., Jr.: Fla. Med. Assoc. *56*:705 (Sept.) 1969.

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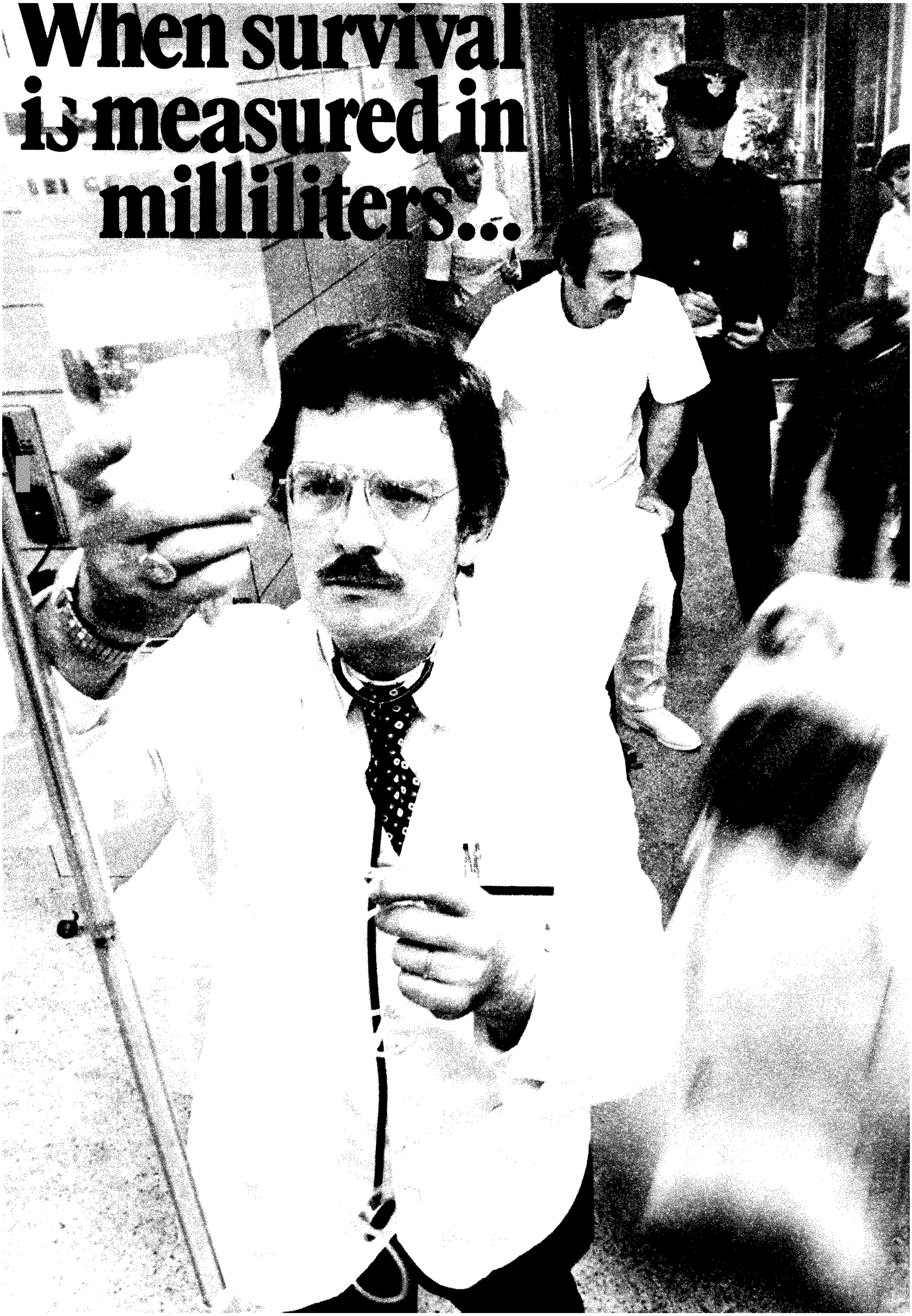
When survival is measured in milliliters...

Moments and milliliters... both are critical in treating hypovolemic shock since survival depends on the rapid, efficient restoration of circulating blood volume. Also crucial is the volume expander you use "stat." Rheomacrodex starts to work immediately to restore blood volume and adequate tissue perfusion.

Greater Initial Plasma Volume

In a recent study,[1] plasma volume expansion and cardiac output were measured in 36 patients with moderate or severe degrees of shock and in eight healthy subjects before, during and after infusion with 500 ml 10% dextran 40, whole blood, 6% dextran 70, plasma, and 5% dextran 40. The greatest plasma volume expansion was established in the 24 shock patients treated with Rheomacrodex. Peak plasma volume increases were more than one liter above controls. Plasma volumes decreased slowly as urinary output increased. Other studies also show the superiority of Rheomacrodex over blood, plasma, saline or lactated Ringer's for increasing initial plasma volume.[2–5]

Improved Cardiac Output

Measurement of hemodynamic effect revealed increased cardiac output directly related to increased volume expansion. Peak C.O. values occurred 15 minutes after Rheomacrodex infusion. In patients with moderate or severe degrees of shock, 10% dextran 40 increased cardiac output an average of 70% above control values.[1] Rheomacrodex improves hemodynamics — restores effective cardiac output and tissue perfusion — better than whole blood, plasma or clinical dextran.

Increased Tissue Perfusion

Restoring blood pressure often is not enough to reverse shock. Most important is the maintenance of adequate tissue perfusion. Rheomacrodex achieves this by decreasing red blood cell aggregation to a greater extent than crystalloids, blood or plasma.[6–10] This improvement in microcirculatory blood flow is reflected in increased oxygen availability and consumption, a vital contribution to the reversal of shock.[11]

Delayed Renal Excretion

In hypovolemia, delayed renal clearance tends to prolong the colloid osmotic effects of Rheomacrodex.[1] During infusion, Rheomacrodex is evenly distributed in the vascular system. The plasma concentration of dextran falls rapidly during the first hour as smaller molecules are excreted. Generally, 70% of Rheomacrodex infused in normovolemic subjects is excreted via the kidney in 24 hours.[12] Excretion is then slowed as the higher molecular weight fraction of dextran remains in the circulation to be metabolized at the rate of 70-90 mg/kg body weight per 24 hours.

Guidelines for Use

1. May be administered on a "response to therapy basis" up to 1,500 ml initially in first 24 hours.
2. Infuse first 500 ml within 30 minutes.
3. To support blood volume beyond 24 hours, administer 500 to 1,000 ml daily.
4. Do not continue beyond five days.
5. May be given with whole blood.
6. Keep patient well hydrated. Increase hydration if urine flow drops below 50 ml/hour.
7. Can be given to any patient without blood typing. However, blood should be drawn prior to infusion for future testing.

REFERENCES: **1.** Shoemaker, W.C. and Monson, D.O.: Surg. Gynec. Obstet. 137:453, 1973. **2.** Ahnefeld, F.W. et al.: Anaesthesist 14:137 (May) 1965. **3.** Gelin, L.E. et al.: Acta Chir. Scand. 122:309, 1961. **4.** Gruber, U.F. et al.: Proc 10th Cong Int Soc Blood Transf., 1965, pp. 1116-1119, S. Karger, Basel (Switzerland). **5.** Gruber, U.F. et al.: Symposium on Rheomacrodex I (1964), pp. 13-23. **6.** Mainardi, L.C. et al.: Surgery 56:349 (Aug.) 1964. **7.** Martinovic, N. and Melrose, D.: J. Cardiovasc. Surg. 4:610 (Aug.) 1963. **8.** Suzuki, F. et al.: Ann. Surg. 160-263 (Aug.) 1964. **9.** Baker, R.J. et al.: Arch. Surg. 90:538 (Apr.) 1965. **10.** Baker, R.J. et al.: Arch. Surg. 89:373 (Aug.) 1964. **11.** Mohr, P.A. et al.: Circulation 39:379 (1969). **12.** Arturson, G. and Wallenius, G.: Scand. J. Clin. Lab. Invest. 16:81, 1964.

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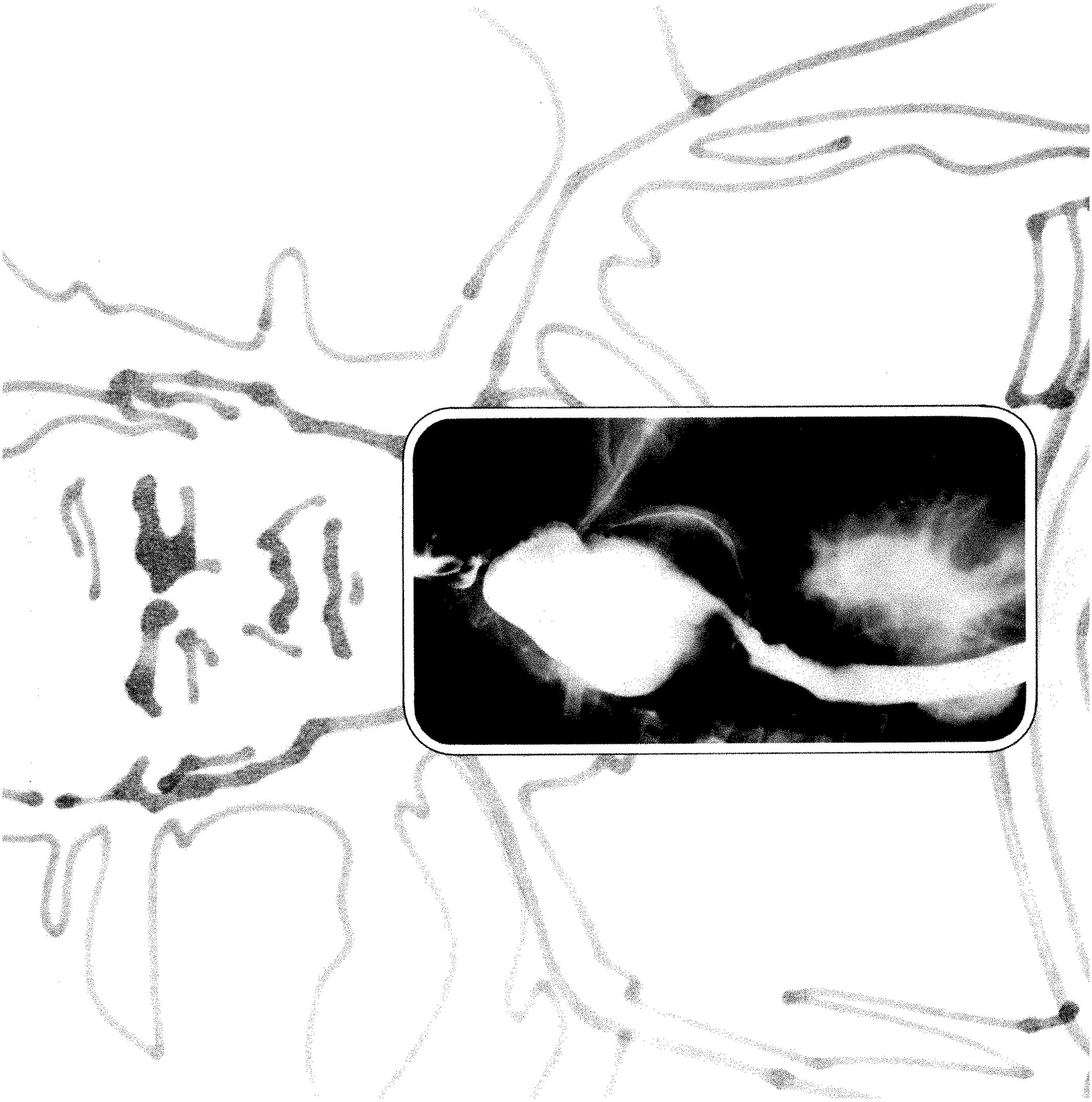
X-ray studies showed a massive cricopharyngeal diverticulum, extending down to the level of the aortic arch. No other abnormal conditions were found.

Surgical treatment: At operation the opening at the back of the esophagus was found to be about 2 inches in diameter. Extremely dense adhesions surrounded the diverticulum, and resection was accomplished only with



considerable difficulty. The excised tissue showed evidence of chronic inflammation, but no tumor was seen. A Levin tube was threaded through the esophagus under direct vision, and a Penrose drain was placed in the incision. The patient withstood the procedure very well.

Postsurgical course: For 3 days following the surgery, the wound seemed to heal normally; the patient was swallowing well, and his condition improved daily. However, when the Penrose drain was removed, an inflamed fistulous tract was discovered in the wound. An antibiotic and streptokinase-streptodornase were administered. Drainage from this opening continued for about 10 days.

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Traumatic Hemobilia

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JAMES C. THOMPSON, M.D., JAY C. FISH, M.D.

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IN 1948, SANDBLOM[22] COINED THE TERM "traumatic hemobilia" and defined the clinical syndrome. At that time he stated that Owen was the first to report such a case a century before. Recently Sandblom[23] has discovered that Francis Glisson was, in fact, the first to describe a case of traumatic hemobilia. Despite many reports of this fascinating and unusual injury, the diagnosis is still usually missed in the early phases of the disease. The variable, and at times protracted interval between the injury and the first hemorrhage tends to obscure the relationship of the two. Additionally, the common causes of gastrointestinal bleeding are seen with such frequency that this rare lesion is not often considered.

Since a previous review from this institution in 1969,[7] we have treated two additional patients with traumatic hemobilia. The purpose of this report is to describe these cases and to summarize the reported experience with this condition in the last four years.

Case Reports

Case 1. A 36-year-old man was involved in an automobile accident in March 1972. He was operated upon for an extensive liver injury. He was in the hospital for 27 days during which time he received multiple blood transfusions. One week after discharge he was readmitted with fever and symptoms that were suggestive of a partial small bowel obstruction. These symptoms subsided with conservative management. In June 1972 he experienced two episodes of gastrointestinal bleeding preceded by severe epigastric pain which lasted for several minutes. After both episodes, barium studies of the upper gastrointestinal tract were interpreted as normal. In July 1972, following another hemorrhage, he was referred to the University of Texas Medical Branch Hospitals.

There were no remarkable physical findings on admission. The laboratory data were as follows: hemoglobin 10 gm/100 ml, white blood count 8,900/mm,[3] alkaline phosphatase 325 mμ/ml (30–120 mμ/ml normal). All other laboratory studies were within normal limits. Hepatic arteriography revealed a small aneurysm within the liver substance near the porta hepatis (Figs. 1 & 2). The vessels in the right lobe were splayed around a large filling defect. Liver scan confirmed the presence of a large mass in the anterior, superior aspect of the right lobe. Upper gastrointestinal series, barium enema and endoscopic examination of the esophagus, stomach and proximal duodenum were normal.

A diagnosis of traumatic hemobilia was made and an operation was performed on July 17, 1972. A cavity was found between the liver and the right hemidiaphragm which communicated through a small opening with a larger cavity deep within the substance of the liver. Approximately 1,000 ml of necrotic liver tissue and clotted blood were evacuated. No active bleeding sites were identified. The omentum was packed into the cavity and drains were placed. Bile drained from the cavity for ten days postoperatively. The patient recovered uneventfully, returned to work, and has remained without symptoms.

Comment

This case indicates that if traumatic hemobilia is to be recognized, it is necessary to consider the possibility that gastrointestinal bleeding may be related to previous liver injury.

Case 2. A 28-year-old man sustained blunt injuries to the head, right lower chest and upper abdomen in an automobile accident on August 3, 1972. He did not lose consciousness and he was not hospitalized after the accident. Two weeks later he had the sudden onset of epigastric pain followed by hematemesis and melena. For this and two subsequent episodes of upper gastrointestinal hemorrhage during the next four weeks, he was admitted to his local hospital and transfused with a total of 10 units of blood. Routine diagnostic studies for a gastroduodenal source of the bleeding was negative. The only positive findings were nonvisualization of the gallbladder on oral cholecystography and a serum bilirubin of 3.0 mg/100 ml. Following the last hemorrhage, he was transferred to the University of Texas Medical Branch Hospitals with the diagnosis of post-traumatic hemobilia made by his referring physician.

The only physical finding of significance was tenderness in the epigastrium. The laboratory data included the following: hemoglobin 10.5 gm/100 ml, white blood count 12,700/mm,[3] total

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* Jeanne B. Kempner Fellow.

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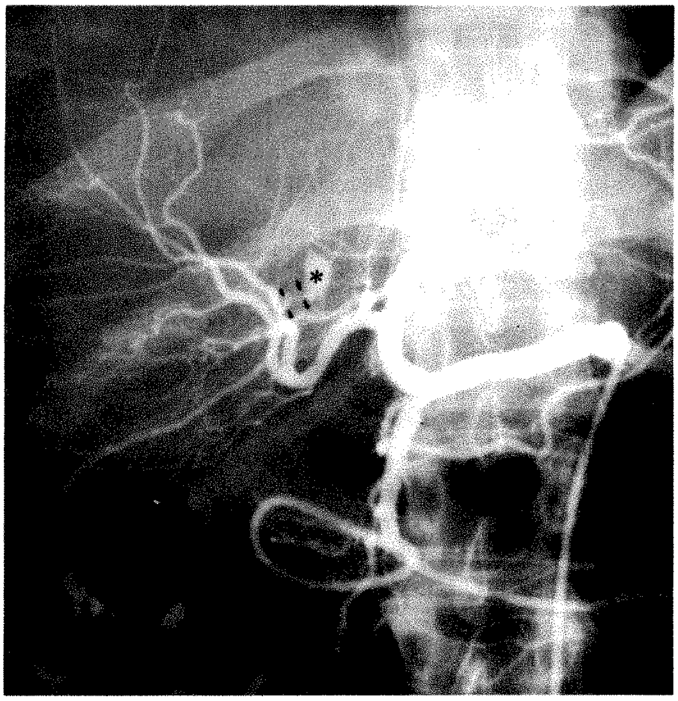


FIG. 1. Arterial phase.

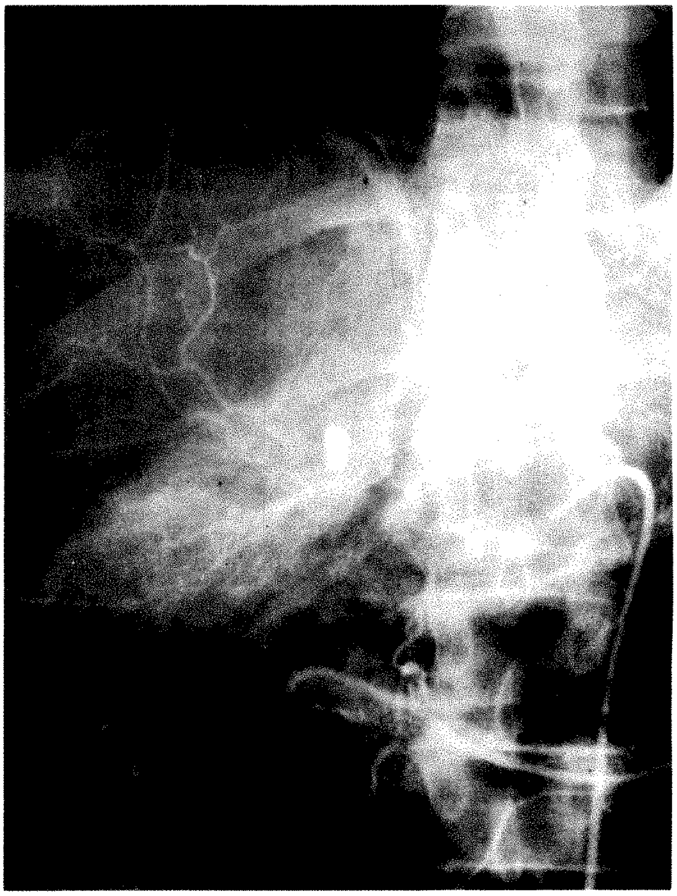


FIG. 2. Venous phase.

FIGS. 1 & 2. Arterial venous phases of hepatic arteriography demonstrate a small intrahepatic aneurysm. The precise origin could not be determined. Intrahepatic vessels are stretched and compressed by a large mass in the right lobe.

bilirubin 3.8 mg/100 ml, alkaline phosphatase 345 mμ/ml, SGOT 120 mμ/ml (10–40 mμ/ml normal), SGPT 157 mμ/ml (10–50 mμ/ml normal). All other laboratory studies, as well as chest x-ray and upper gastrointestinal series, were normal. Hepatic arteriograms revealed the presence of an avascular mass in the center of the right lobe of the liver with a pseudoaneurysm measuring 2.5 × 3.5 cm in diameter (Figs. 3 & 4). The liver scan demonstrated a space-occupying lesion between the right and left lobes of the liver.

An exploratory laparotomy was performed on September 27, 1972. The liver was enlarged and there was a firm mass bulging from the superior portion of the anterior surface of the right lobe. The incision was carried into the right chest to gain adequate exposure. The mass was incised and found to contain 200 ml of old blood clots and necrotic hepatic tissue under great pressure. After evacuation of this material, brisk, pulsatile bleeding was seen to originate from a branch of the right hepatic artery. The point of bleeding was ligated with complete control of hemorrhage. A rent in the right intrahepatic biliary duct was repaired. The gallbladder was filled with blood clots. These were evacuated and a cholecystostomy tube was inserted. The cavity in the right lobe of the liver was packed with omentum and adjacent drains were placed.

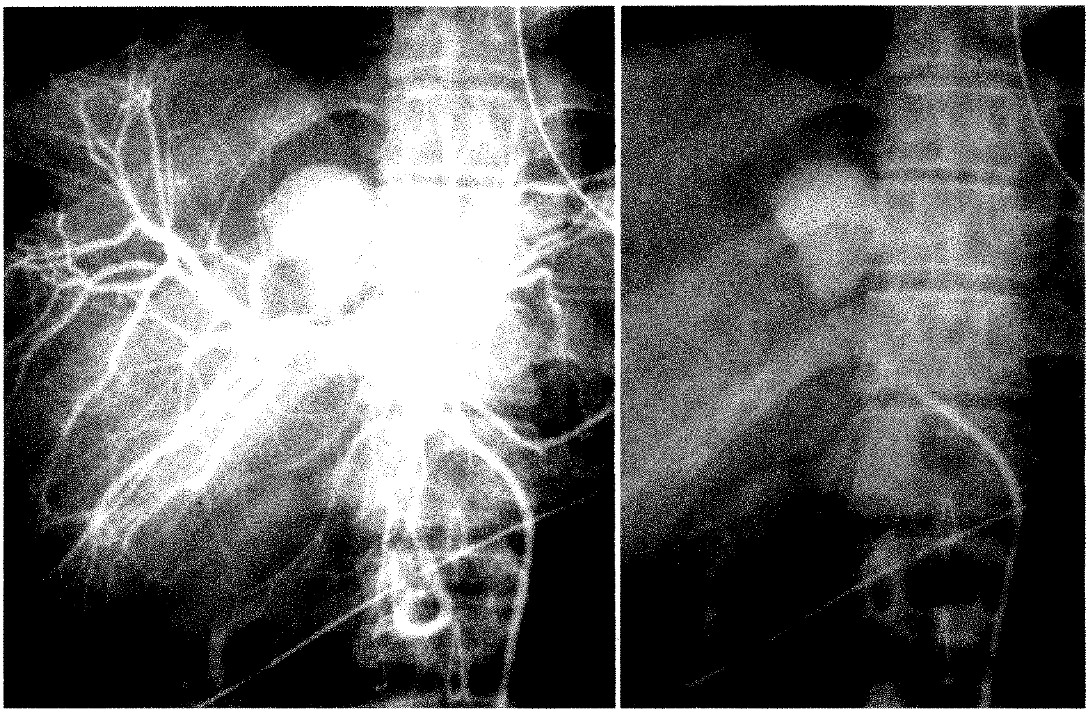
The postoperative course was uncomplicated except for a small right pleural effusion. The patient has returned to work and is asymptomatic at the present time.

Comment

This case illustrates that hemobilia may occur after seemingly insignificant abdominal trauma. The history of blunt abdominal trauma with subsequent gastrointestinal bleeding and the absence of any prior symptoms of peptic ulcer disease led to the correct diagnosis. Hepatic arteriography and liver scan confirmed the diagnosis and the site of injury. At operation it was possible to visualize and repair directly the rents in the intrahepatic artery and bile duct.

Review of Literature

Our survey of the English literature from 1969 through 1972 yielded reports of eight patients[5,12,26,31,43,44] to add to the 59 patients whose findings were summarized in 1969.[7] Addition of the two patients in this report gives a total of 69 reported cases. No patients in whom hemobilia developed after operations on the extrahepatic biliary tract or after percutaneous liver biopsy, or in whom hemobilia was a consequence of nontraumatic lesions are included in this report. Sandblom has recently published a monograph on over five hundred cases of hemobilia due to many different causes.[23] Blunt trauma is the most common cause of traumatic hemobilia (Table 1). The injury was of such severity that nearly all patients required operation at the time. The initial hepatic injuries were managed in various ways (packing, debridement, ligation). Hemorrhage occurred one day to two years after injury, with an average interval of one



FIGS. 3 (left) & 4 (right). A large pseudoaneurysm in the right lobe of the liver can be seen in both arterial and venous phases of selective arteriography.

month (Fig. 5). Significant delay frequently occurred between onset of hemorrhage and definitive treatment (Fig. 6). Delay was nearly always due to a failure to recognize that the liver can be the site of major gastrointestinal hemorrhage. In some patients, the previous history of abdominal trauma was either overlooked or dismissed as inconsequential. Further delays undoubtedly occurred because the hemorrhage was usually limited and intermittent. Conventional upper gastrointestinal studies are not diagnostic in patients with hemobilia and time may be wasted on repeated examinations in search of a duodenal or gastric ulcer. Upper gastrointestinal bleeding in patients whose negative barium radiologic studies demonstrate no lesion is often ascribed to stress ulcers. When jaundice occurs, it is often attributed to serum hepatitis or to hemolysis associated with massive transfusions.

In patients with traumatic hemobilia, initial trauma causes rupture of liver parenchyma with or without extension to Glisson's capsule. The initial management of liver injuries is an important factor in the pathogenesis of hemobilia. If all necrotic liver is not removed or if deep wounds are closed only superficially, the stage is set for the subsequent development of hemobilia. The basic lesion in hemobilia is a potential cavity filled with clot or ischemic liver. Further necrosis of ischemic tissue leads to arteriolar hemorrhage, with subsequent enlargement of the cavity leading to further pressure necrosis and erosion into the biliary system. Blood may then enter the biliary tree and pass into the duodenum. Biliary colic occurs due to obstruction of the bile ducts by clots. Relief of pain is usually coincident with the development

TABLE 1. *Hemobilia: Mechanism of Injury*

	No.	Deaths
Non-Penetrating	58	12
Penetrating	11	1
	69	13

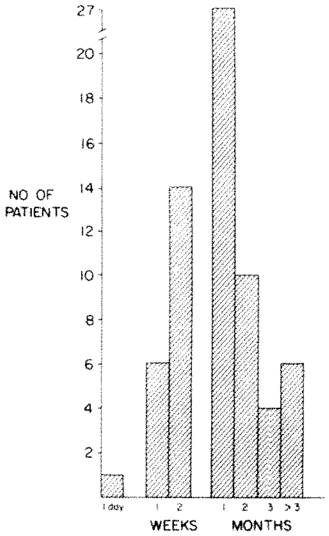


FIG. 5. Hemobilia: Time between injury and first hemorrhage.

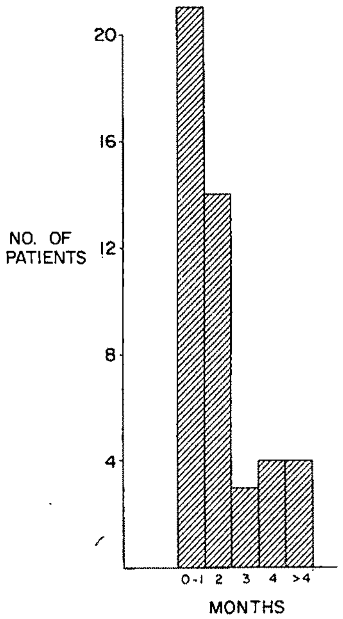


FIG. 6. Hemobilia: Time between first hemorrhage and definitive treatment.

of gastrointestinal hemorrhage, manifested by hematemesis or melena, or both, depending on the size of the hemorrhage. Jaundice may occur depending upon the duration of biliary tract obstruction. Although fever may be present, there have been no reports of cholangitis associated with ductal obstruction. Physical examination is generally unrewarding unless a fistula between a major intrahepatic branch of the hepatic artery and portal vein is present.[5] Tenderness and a palpable mass in the right upper quadrant are present occasionally.

The diagnosis of traumatic hemobilia is not difficult if the clinical triad of pre-existing abdominal trauma followed by colicky abdominal pain and upper gastrointestinal hemorrhage is considered. Evaluation should include barium contrast radiography of the esophagus, stomach, and duodenum to exclude peptic ulcer disease and other common causes of upper gastrointestinal hemorrhage. The serum bilirubin and alkaline phosphatase are often elevated. Once the possibility of hemobilia is considered, hepatic angiography and liver scan are useful in confirming the diagnosis, localizing the lesion to the appropriate area within the liver, and demonstrating the variations of hepatic arterial anatomy.

Treatment of traumatic hemobilia may be divided into five basic categories (Table 2). Debridement of the liver cavity must be thorough in all instances. This may reveal a source of hemorrhage that can be ligated. Occasionally, no active hemorrhage will be found, as in Case 1, and simple drainage after complete debridement will allow the cavity to collapse. Only four of 18 patients treated in this manner rebled, and there were no deaths.

Hepatic artery ligation has recently been popularized by Mays[18] and Madding and Kennedy[14,15] in the treatment of major liver injuries. The preferred site of ligation is proximal to the gastroduodenal artery, which allows for significant liver blood flow via collaterals, while at the same time decreasing the hepatic arterial pressure sufficiently to stop hemorrhage. Madding and Kennedy[15] have used intraoperative and postoperative glucagon infusion in order to increase portal venous blood flow after ligation of the hepatic artery. It appears that hepatic artery ligation performed in this way is safe in the patient with normal liver function, but it should not be used in patients with pre-existing disease such as portal cirrhosis. No deaths have been reported following hepatic arterial ligation for hemobilia.

Hepatic resection should be reserved for those patients with major destruction or necrosis of the right or left lobes, or when the above measures are unsuccessful. Resection is associated with increased mortality (four deaths in 14 patients, Table 2). The principal reason for this is probably that those patients who require resection have a more severe injury, and the mortality rate serves to emphasize that resection should not be undertaken lightly.

The use of gauze packing as definitive therapy should be condemned. Madding and Kennedy,[14] as well as others, have emphasized the increased frequency of both delayed hemorrhage and infection as complications of this treatment in all types of liver wounds. Five of nine patients treated in this manner had recurrent hemorrhage and two died.

The category of no treatment includes patients in whom the diagnosis of hemobilia was made but no definitive treatment was performed. Also included are those who have only indirect types of procedures such as cholecystectomy, cholecystostomy, or T-tube drainage of the common bile duct. Cholecystostomy in conjunction with definitive therapy may be indicated if the gallbladder appears inflamed or grossly distended with blood clots (Case 2). Recently Hendren [12] has reported two patients with hemobilia who required no operation and in whom healing was demonstrated by serial arteriography. The overall result of ten deaths in 19 patients in this group indicates that a more aggressive approach is usually needed to achieve success.

	None	Packing	Debridement	H.A. Ligation	Resection
No.	19	9	18	12*	14
REBLED	0	5	4	3	1
DEATHS	10	2	0	0	4

* ONE CASE TREATED BY ENDOANEURYSMORRHAPHY OF AN HEPATIC ARTERY ANEURYSM

TABLE 2. Hemobilia: Treatment and results.

Summary

We have treated two patients with traumatic hemobilia, and have collected eight more cases to be added to the 59 cases previously reviewed 4 years ago.[7]

From this review, several important conclusions must be made.

1) There is a variable, often extended, delay between the time of hepatic injury and the time of the initial hemorrhage.

2) Further delay in diagnosis commonly occurs after the initial hemorrhage because of failure to relate the gastrointestinal hemorrhage to the previous liver injury, as well as failure to recognize the liver as the site of bleeding.

3) The cornerstone of treatment is debridement of necrotic liver and control of hemorrhage either directly or by hepatic artery ligation. Major hepatic resection may be required. Of 44 patients treated by these means, only eight hemorrhaged again. Four deaths occurred in 14 patients treated by major hepatic resection.

4) Simple packing of the area of injury, or no treatment, resulted in death in 12 of 28 patients. These methods of treatment are unacceptable.

Acknowledgment

We wish to acknowledge the help of Dr. D. L. Cisneros who made the correct diagnosis and referred the patient described in Case 2.

References

1. Amerson, J. R. and Ferguson, I. A.: Traumatic Hemobilia. Surgery, **54**:729, 1963.
2. Bremer, E. H. and Dowli, A.: Traumatic Hemobilia. Amer. Surg., **32**:333, 1966.
3. Broker, H. M. and Hay, L. J.: Hemobilia Following Blunt Trauma to the Liver. Minn. Med., **38**:333, 1955.
4. Burnett, W. E., Rosenmond, G. P., Coswell, H. T. and Hall, J. H.: Unusual Case of Gastrointestinal Hemorrhage. Surgery, **26**:1044, 1949.
5. Cleveland, R. J., Jackson, B. M., Newman, P. H. and Nelson, R. J.: Traumatic Intrahepatic Hepatic Artery—Portal Vein Fistula with Associated Hemobilia. Ann. Surg., **171**:451, 1970.
6. Engler, H. H., Zavaleta, A. A. and Moretz, W. H.: Hemobilia. Amer. Surg., **30**:756, 1964.
7. Fish, J. C. and Nippert, R. H.: Traumatic Hemobilia: The Dilemma of Delay. J. Trauma, **9**:546, 1969.
8. Gunderson, A. E. and Green, R. M.: Traumatic Hemobilia: Accurate Preoperative Diagnosis by Hepatic Artery Angiogram. Surgery, **62**:862, 1967.
9. Guynn, V. L. and Reynolds, J. T.: Surgical Management of Hemobilia. Arch. Surg., **83**:73, 1961.
10. Hendren, W. H., Warshaw, A. L., Fleischil, D. J. and Bartlett, M. K.: Traumatic Hemobilia: Non-operative Management with Healing Documented by Serial Angiography. Ann. Surg., **174**:991, 1971.
11. Hermann, R. E. and Hoerr, S. O.: Aids in the Diagnosis of Traumatic Hemobilia. Surg. Gynecol. Obstet., **125**:55, 1967.
12. MacKay, A. G. and Page, H. G.: Hematemesis Associated with Hemobilia. New Engl. J. Med., **260**:468, 1959.
13. Mac Vaugh, H., Haupt, G. J., Myers, R. N. and Daly, J. W.: Traumatic Hemobilia. Surgery, **60**:547, 1966.
14. Madding, G. F. and Kennedy, P. A.: Trauma to the Liver. Philadelphia, W. B. Saunders Co., 1971.
15. Madding, G. F. and Kennedy, P. A.: Hepatic Artery Ligation. Surg. Clin. N. Amer., **52**:719, 1972.
16. Manos, A.: Rare Case of Traumatic Hemobilia. Internat. Abst. Surg., **107**:376, 1958.
17. Markgrof, W. H.: Traumatic Hemobilia Associated with a Hepatoportal Biliary Fistula. Arch. Surg., **81**:860, 1960.
18. Mays, E. T.: Lobar Dearterialization for Exsanguinating Wounds of the Liver. J. Trauma, **12**:397, 1972.
19. Poulos, E.: Traumatic Hemobilia Treated by Massive Liver Resection. Arch. Surg., **88**:596, 1964.
20. Reinhardt, G. F. and Hubay, C. A.: Surgical Management of Traumatic Hemobilia. Amer. J. Surg., **121**:238, 1971.
21. Saliba, N., Sawyer, K. C. and Sawyer, K. C. Jr.: Traumatic Hemobilia. Arch. Surg., **82**:298, 1961.
22. Sandblom, P. H.: Hemorrhage into the Biliary Tract Following Trauma—"Traumatic Hemobilia." Surgery, **24**:571, 1948.
23. Sandblom, P. H.: Hemobilia. Springfield, Charles C. Thomas, 1972.
24. Schatzki, S. C.: Hemobilia. Radiology, **77**:717, 1961.
25. Sedgqick, C. E. and Coburn, R. J.: Evaluation of the Patient with Hemobilia. Surg. Clin. N. Amer., **50**:683, 1970.
26. Shohl, T.: Hepatic Artery Ligation for Massive Hemobilia. Surgery, **56**:855, 1964.
27. Souliotis, P. T., Pettegrew, A. H. and Chamberlain, J. W.: Traumatic Hemobilia. New Engl. J. Med., **268**:565, 1963.
28. Sparkman, R. S.: Massive Hemobilia Following Traumatic Rupture of the Liver. Ann. Surg., **138**:899, 1953.
29. Spector, N.: Ligation of the Right Hepatic Artery in Hemobilia. Ann. Surg., **145**:244, 1957.
30. Spencer, F. C., Menguy, R. and Eiseman, B.: Operative Cholangiography in Management of Traumatic Hemobilia. Surgery, 54:376, 1963.
31. Steichen, F. M. and Sheiner, N. M.: Traumatic Intrahepatic Hemobilia. Arch. Surg., **92**:838, 1966.
32. Stone, F. A., *et al.*: Treatment of Exsanguinating Rupture of the Right Lobe of the Liver by Ligation of the Main Hepatic Artery. Ann. Surg., 162:933, 1962.
33. Sworn, B. R.: Traumatic Hemobilia with Severe Haematemesis and Melaena. Brit. J. Surg., **47**:254, 1959–60.
34. Whelan, T. J. and Gillespie, J. T.: Treatment of Traumatic Hemobilia. Ann. Surg., **162**:920, 1965.
35. Wilkinson, G. M., Mikkelsen, W. P. and Berne, C. J.: The Treatment of Post-traumatic Hemobilia by Ligation of the Common Hepatic Artery. Surg. Clin. N. Amer., **48**:1337, 1968.
36. Winchester, D. P., Seed, R. W., Bergan, J. J. and Conn, J. J. Jr.: Jaundice, Hemobilia and Hemoperitoneum. Consequences of Rupture of Hepatic Artery Aneurysm. Amer. J. Surg., **120**:384, 1970.
37. Wright, P. W. and Orloff, M. J.: Traumatic Hemobilia. Ann. Surg., **160**:42, 1964.

Pulmonary Gas Exchange Following Hemorrhagic Shock and Massive Blood Transfusion in the Baboon

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HYPOXEMIA HAS BEEN REPORTED in patients following a combination of nonthoracic trauma, hemorrhagic shock, and anesthesia requiring massive blood transfusion.[2,12,13] Pulmonary microembolization from debris in ACD preserved bank blood has been implicated as one of the causes of this hypoxemia since it has been demonstrated that the number of microaggregates in stored ACD bank blood is markedly higher than in fresh blood and are not removed by a standard 170 micron blood filter.[6–8,10,12,14] An association has been shown between massive transfusion of stored bank blood and progressive pulmonary insufficiency but interpretation of reports of clinical studies of patients with hypoxemia is difficult partly because of multiple etiologies and superposition of complex and variable therapy.[11,12]

Laboratory investigators have demonstrated correlation between infusion of ACD blood and changes in pulmonary vascular pressures in the anesthetized dog model.[4,6,9,15] One study has been published showing increased pulmonary vascular resistance, decreased pO_2 A-V difference and increased end-inspiratory pressure after perfusion of an isolated lung lobe with three-week-old blood in both the baboon and dog.[1] In all of these studies anesthesia, thoracotomy, artificial ventilation and heparinization intrude on our interpretation of results. There are no available controlled studies showing what effect, if any, infusion of stored blood has on arterial blood gases in an unanesthetized primate requiring blood because of hemorrhage. In order to evaluate the possible deleterious role of ACD blood upon pulmonary gas exchange, we designed an experiment to measure changes in arterial blood oxygen tensions after hemorrhagic shock and massive transfusion in an unanesthetized spontaneously breathing baboon.

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Method

Eleven juvenile baboons (Papeo doguera) weighing between 5.0 and 13.6 kg had a left thoracotomy and insertion of a pulmonary artery (PA) and left atrial (LA) catheters which were filled with heparin and secured subcutaneously. At least two weeks later the animals were anesthetized with Sernylan® 1.1 mg/kg, the thoracic catheters exteriorized, two other catheters placed in the femoral artery (FA) and inferior vena cava (central venous pressure line) and a Yellow-Springs thermistor probe inserted either into the rectum or esophagus. The animals were placed in a restraining chair in a reclined position. Six hours after the administration of Sernylan® the animals were awake and alert. Baseline pressure measurements of FA, PA, LA and CVP were recorded

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The experiments were conducted according to the principles enunciated in "Guide for Laboratory Animal Facilities and Care," published by the United States Department of Health, Education and Welfare, Public Health Service.

Reprint requests to Dr. Tobey.

through Hewlett-Packard 267 AC transducers on a Sanborn multi-channel recorder. During spontaneous air breathing duplicate arterial blood samples were obtained and P_aO_2, P_aCO_2 and pH determined with an Instrumentation Laboratories 313 Blood Gas Analyzer.

The five baboons in the experimental group were bled until mean systemic arterial pressure reached 60 mmHg. This pressure was maintained for one hour by withdrawal or infusion of the animal's own blood. Further hemorrhage lowered mean arterial pressure to 40–45 mmHg for an additional hour. No medications were given during the two hour shock period. Resuscitation was accomplished by transfusion of warmed, type-specific baboon blood which had been stored at 2–6°C for 16–21 days in 250 ml Fenwal plastic bags containing ACD solution. After mean systemic arterial pressure had been restored to baseline value and had stabilized ten minutes, an isovolemic exchange transfusion was performed until a total of twice the calculated blood volume (144 ml/kg) had been infused. Calcium chloride 200 mg was given intravenously after each 250 ml of blood transfused. Pressure of 220 mmHg was applied to the bag and one standard blood filter (170 μ pore mesh, blood recipient set, Fenwal Laboratories, Morton Grove, Il) was used for each 500 mls of blood transfused. LA pressure and CVP were monitored so that the pressures were never allowed to rise more than 4 mmHg above baseline values to prevent fluid overload. A blood sample was obtained after passage of the transfused blood through the filter for a particle size distribution analysis as previously described and for blood culture.[14]

Post-transfusion vascular pressures were recorded and duplicate arterial blood gases again determined during spontaneous air breathing.

Within two hours of completion of transfusion, an anesthetic dose of pentobarbital was given and all animals were sacrificed by expansion of the lungs using paraformaldehyde instilled through a cuffed endotracheal tube. In this way, fixation of lung tissue was simultaneous with death.

Necropsy was performed and sections of lung, heart, kidney and liver prepared for both light and electron microscopic examination. Tissue for light microscopic examination was fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned to approximately 5 micron thickness and stained with hematoxylin and eosin. Tissue for transmission electron microscopy was fixed for 2–12 hours in 2% paraformaldehyde buffered with S-collidine. Post fixation was performed with osmium tetroxide. Tissue was stained *en bloc* using uranyl acetate and embedded in Epon. Approximately 600 Angstrom thick sections were cut using a Porter-Blum model II ultramicrotome. Sections were stained with lead citrate and examined in a Siemens Elmoskop II A at 30 KV accelerating voltage.

The observed values for mean arterial pO_2 did not change significantly following shock and transfusion in a preliminary group of six experimental animals. But these animals were found to have undergone a decrease in rectal temperature during the experiment which required the application of human temperature correction factors to the blood gas values. When these temperature corrected values were analyzed, the post-transfusion mean P_aO_2 was then found to be significantly different from mean baseline value. However, we are not certain that rectal temperatures are accurate reflections of blood temperature following shock and we are also uncertain of the appropriate temperature correction factors for stored baboon blood.[5] Therefore, we elected to repeat the experiment and carefully maintain esophageal core temperature at 37°C by surface warming. It is the data from the second experiment which is reported here.

Six baboons served as a control group. They were prepared in the same manner as the experimental group, except that they were not shocked and not transfused. The animals were sacrificed in the same manner as the experimental group and examined pathologically.

In initial studies the size distribution of microaggregates which developed in blood of different species during storage was determined using methods previously described.[14] Two minutes after dilution (1:200) of blood in saline containing saponin (2 gm/l Fisher Scientific), particles larger than leukocytes were measured as 5 ml of continuously stirred suspension passed through a 400 μ aperture of a particle size analyzer (Model T, Coulter Electronics, Hialea, Fl). The results are reported as the mean volume of particles 13–25 μ and 32–80 μ in size. Blood was drawn into 250 ml pediatric plastic bags containing ACD (Fenwal Laboratories, Morton Grove, Ill.) from nine baboons and seven dogs. Particle size distribution measurements were performed immediately after drawing blood and after 21 days of storage at 4°C. The results were compared to measurements made on eight similar units of human blood drawn under standard blood bank conditions. Samples of all units studied were cultured and were free of bacterial contamination.

Statistical analysis was done by applying Student's test to the means and mean differences.

Results

Blood Gases

1. Arterial oxygen tensions are summarized in Table 1. The experimental animals had a mean change of P_aO_2 from 93.0 ± 3.2 to 97.5 ± 4.0 post-transfusion. The Control Group mean P_aO_2 was unchanged with a 92.2 ±

GROUP (N)	BASELINE	POST-TRANSF. OR POST-REST	Δ
SHOCK (5)	93.0 ± 3.2	97.5 ± 4.0	4.5 ± 5.1
CONTROL (6)	92.2 ± 4.6	92.6 ± 4.7	0.4 ± 8.3

TABLE 1. *Arterial oxygen tension changes before and after shock and transfusion or rest period in mmHg. (mean ± S.E.)*

4.6 mmHg and 92.6 ± 4.7 mmHg for baseline and post-rest oxygen tensions respectively. A comparison of means and of mean changes revealed no statistically significant difference between the two groups.

2. Post-transfusion and post-rest mean P_aCO_2 decreased in both the Experimental and Control Groups from their baseline value. Thus, the Experimental Group mean P_aCO_2 changed from a baseline of 35.1 ± 2.7 mmHg to 31.8 ± 2.2 mmHg; and Control from 38.1 ± 1.8 mmHg to 33.3 ± 2.8 mmHg. No significant differences were found in the means of the Experimental Group or Control Group nor was there any significant difference in the mean changes between the two groups. Results are summarized in Table 2.

3. In both groups comparison of baseline pH with the post-transfusion (or post-rest) values showed no significant difference.

Vascular Pressures

In general all mean vascular pressures were lower at post-transfusion or post-rest period than during the baseline period but the changes were not statistically significant. Mean femoral artery pressure decreased from a baseline of 113 ± 7 mmHg to 106 ± 9 mmHg in the Experimental Group; and from 122 ± 6 mmHg to 121 ± 5 mmHg in the Control Group. Likewise, pulmonary artery pressures were lower after the transfusion or rest period than at baseline. Experimental Group mean PA pressure declined from 9.0 ± 3 to 8.5 ± 2.9 mmHg; and Control Group from 10.8 ± 2 mmHg to 9.0 ± 1 mmHg. Left atrial and central venous pressure changes were also not significantly different. All mean vascular pressure changes are summarized in Table 3.

Particle Counts

Particle counts for size and distribution confirmed the similarity of the stored ACD baboon blood to that of stored ACD human blood. The cumulative volume of particles (13–80 μ) in human blood immediately after drawing was $45 \pm 6 \times 10^3$ μ^3/mm^3 and did not differ significantly from blood drawn similarly from the baboon and dog. However, on day 21 the size distribution of the microaggregates in dog blood was significantly different ($P < 0.05$) from human and baboon blood with fewer medium-sized particles. The results are summarized in Table 4.

Pathology

Histologic changes revealed by light microscopy included focal minimal capillary and arteriolar endothelial swelling in all tissues examined. There was mild to moderate pre-existing diffuse interstitial pulmonary fibrosis apparently due to infestation by the lung mite (*Pneumonssus semicola*) in all groups. In two animals of the Experimental Group single recent ante-mortem thrombotic occlusions of a small pulmonary artery were detected.

Transmission electron microscopy provided results similar to light microscopy with the following exceptions: 1, no vessels occluded by thrombi or emboli were observed; 2, in two animals from the Experimental Group strands of fibrin were present in arterioles, capillaries and venules of lung and kidney (Fig. 1). The fibrin strands occurred singly or in groups containing up to six strands. Individual fibrin strands generally had blunt ends with partial obscuration of their characteristic periodicity. This was considered to be the result of ante-mortem degeneration rather than autolysis because of satisfactory fixation of adjacent structures.

Discussion

Hypoxemia has been shown to occur in patients after shock and massive transfusion.[2,8,10-13] McNamara *et al.*[10] have shown a significant relationship between low arterial oxygen tension and large volumes of transfused blood in battle casualties during the first 48 hours after injury and resuscitation. He has also found elevated screen filtration pressures in blood samples from combat casualties during infusion of aged ACD blood.[10] Hisson and Swank[6] have correlated increased screen filtration pressure with the debris formed in stored ACD blood. This debris forms microaggregates which are not removed by the standard 170 micron filter and when infused into patients is thought to be partially filtered by the pulmonary capillary bed.[6,7,10] On this basis it has

GROUP (N)	BASELINE	POST-TRANSF. OR POST-REST	Δ
SHOCK (5)	35.1 ± 2.7	31.8 ± 2.2	3.3 ± 1.3
CONTROL (6)	38.1 ± 1.8	33.3 ± 2.8	4.8 ± 3.7

TABLE 2. *Arterial carbon dioxide tension changes before and after shock and transfusion or rest period in mmHg. (mean ± S.E.)*

TABLE 3. *Vascular pressures before and after shock and transfusion or rest period in mmHg. (mean ± S.E.)*

PRESSURE MEASUREMENT SITE	SHOCK (5)			CONTROL (6)		
	BASE-LINE	POST-TRANSF.	Δ	BASE-LINE	POST-REST	Δ
FEMORAL ARTERY	113 ± 7.2	106 ± 8.6	7 ± 10.3	122 ± 5.9	121 ± 5.4	0.8 ± 4.0
PULMONARY ARTERY	9.0 ± 2.3	8.5 ± 2.9	0.5 ± 3.0	10.8 ± 1.5	9.0 ± 0.7	1.8 ± 1.0
LEFT ATRIUM	-1.0 ± 1.0	-1.0 ± 0.8	0.0 ± 0.8	-0.8 ± 2.6	-1.2 ± 2.6	0.4 ± 3.6
CENTRAL VENOUS	-0.4 ± 0.6	-1.0 ± 0.7	0.6 ± 1.1	2.7 ± 1.6	-1.1 ± 4.0	3.8 ± 3.7

been speculated that blood transfusion causes pulmonary microembolization which, in turn, may lead to pulmonary insufficiency and hypoxemia.

The clinical occurrence of pulmonary microemboli after large volume transfusion has been reported by several investigators.[2,7,10,11] Jennevein and Weiss[7] found microemboli in the lungs of their patients who had received massive transfusions associated with cardio-pulmonary by-pass. However, no pulmonary function measurements were done. Moseley and Doty[11] reported progressive fatal respiratory insufficiency in two patients following severe combat wounds and massive blood transfusion (one patient received 27 units, the other 97 units). Both patients had low arterial oxygen tensions and post-mortem evidence of pulmonary microembolization. Simmons *et al.*[12] reported that patients admitted in hemorrhagic shock and who had received more than 4000 mls of blood had a higher incidence of hypoxemia during convalescence than those who were not in shock or had received less than 4000 mls of blood. In the clinical setting of major trauma, post-anesthetic atelectasis, respiratory splinting secondary to pain, narcotic-induced respiratory depression, fat embolization, fluid overload, fever and pneumonitis are common. Thus, it is difficult to isolate the influence of these factors on respiratory function from shock and massive transfusion.

Reports[4,6] of laboratory experiments in the dog have clearly documented an increase in pulmonary vascular pressure associated with the infusion of stored ACD blood. McNamara *et al.*[9] also found elevated pulmonary vascular resistance in the dog lung perfused with 3-week-old blood but no increase in resistance in the opposite lung simultaneously infused with fresh blood. But in none of these experiments was the lung's capacity for gas exchange measured. Cook and Webb[4] found that P_aO_2 was normal in dogs during shock, became elevated immediately after resuscitation with shed blood, and returned to normal four hours post-shock.

Our findings in the baboon indicate no dysfunction in the capability of the lung to maintain P_aO_2, P_aCO_2 and pH after a period of severe shock and massive exchange transfusion. The conditions of our experiment provided a severe stress to the animals since mortality of the shock period was about 50% and the amount of transfused blood in the baboon is comparable to a twenty unit transfusion in a 70 kg man. Furthermore, comparison of particle size and distribution demonstrates that stored baboon blood is definitely more similar to stored human blood than is the dog. This is consistent with the findings by others that SFP of dog blood is

GROUP (N)	SMALL (13 - 25 μ)	MEDIUM (32 - 80 μ)
HUMAN (8)	213 ± 20	145 ± 31
BABOON (9)	229 ± 55	223 ± 45
DOG (7)	155 ± 44	51 ± 19*

*COMPARED TO HUMAN $p < 0.05$

TABLE 4. *Cumulative volume of particles (expressed in units × 10^3 μ^3/mm^3) at 21 days of storage in ACD at 4°C of human, baboon and dog blood. (mean ± S.E.)*

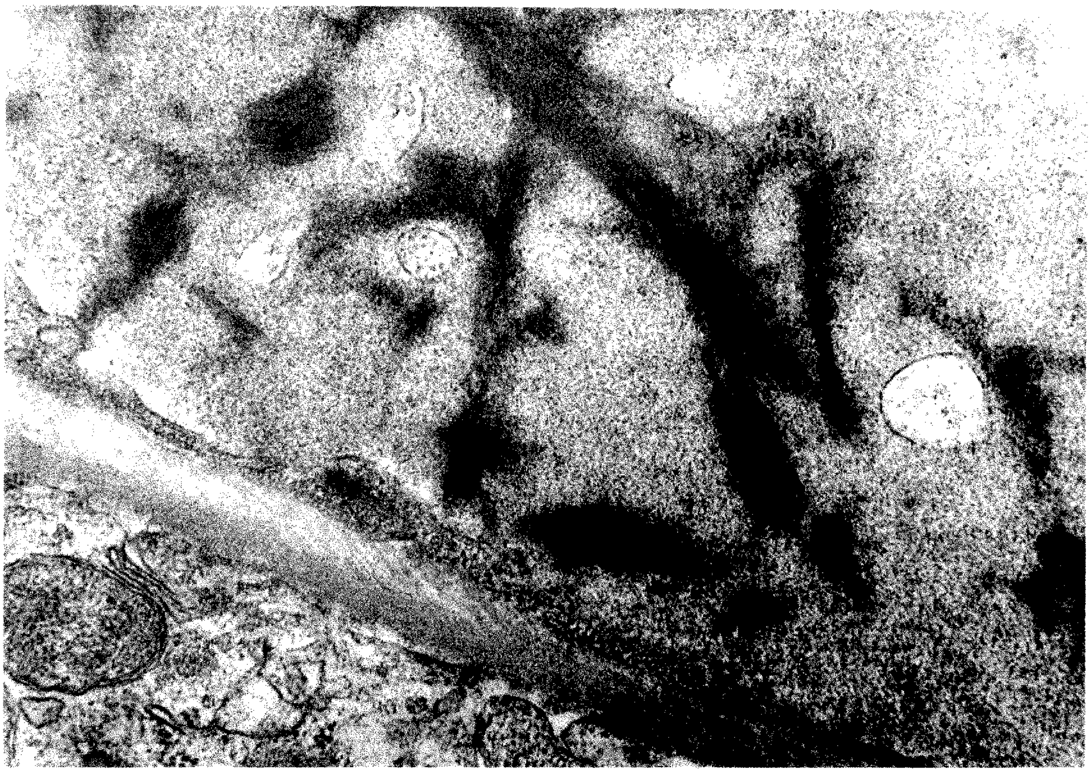

FIG. 1. Kidney: degenerated fibrin is present in an interstitial cortical vessel. 54,000 ×

low after storage compared to human and baboon blood.[1,9]

In the report by Bennett *et al.*,[1] a downward change in arteriovenous pO_2 gradient was found in the isolated lung of both the baboon and dog when either 1-day-old or 3-week-old blood was perfused. The gradient decrease was greater during the three-week-old blood perfusion but this change was not statistically significant in the baboon. These findings are not at all inconsistent with our results since our experimental animals were not anesthetized, were breathing spontaneously and had recovered from their thoracotomies. Thus, they were capable of hyperventilating, changing cardiac output and pulmonary vascular resistance in a more normal physiologic manner in order to maintain normal blood gases. Bennett *et al.*'s animals were anesthetized, were ventilated by mechanical means with a constant volume and had a thoracotomy as part of the preparation for the experiment. Besides the detrimental pulmonary effects of these preparations, increased ventilation demanded by a change in V_D/V_T was not possible.

Since our findings show that shock and massive transfusion did not lead to a detectable impairment in pulmonary gas exchange, it is important to determine how large an impairment we might have failed to detect. In order to estimate this we computed 95% confidence intervals using a one-tail "t" statistic to estimate maximum likely changes from baseline. This indicated a maximum drop of 7 mmHg in arterial O_2 tension which might have been undetected. When the changes from baseline of the Experimental Group were compared with the changes from baseline of the Control Group the maximum difference was 5 mmHg. This figure is slightly smaller than the previous one because of the larger degrees of freedom associated with the pooled estimate of variance used in the second contract. Should subsequent work show for example that control arterial P_aO_2's remain unchanged at 90 mmHg during the experiment, while the experimental group falls from 90 to 85, this would not be inconsistent (0.05% level) with our findings.

During the infusion of blood, mean PA pressure was never elevated above 14 mmHg in any animal and mean PA pressures in both groups were decreased within thirty minutes of completion of the transfusion. The discrepancy between this data and that reported by Bennett *et al.* can be explained by difference in experimental design.[1] In the Bennett study a progressive significant increase in pulmonary vascular resistance occurred during the course of perfusion of the lung in both the baboon and dog. But again their experimental protocol created an artificially constant blood flow and maintained the venous pressure at zero. Our animals were intact and capable of normal physiologic changes in response to a stimulus.

Our microscopic findings are different from reports based on both dog and baboon investigations. In the report by Connell and Swank[3] diffuse occlusion of pulmonary microcirculation was observed in all dogs after hemorrhagic shock and in all non-shocked dogs which received ACD preserved blood transfused through a standard filter. Since the dogs were heparinized they did not have fibrin present in the vessels. Bennett and coworkers[1] observed marked changes in the perfused isolated baboon lung. They found interstitial edema, perivascular and alveolar hemorrhage, intra-alveolar fluid and alveolar septal congestion. In contrast we found pulmonary arterial thrombi probably of embolic origin in lung sections of only two of the shocked and transfused baboons. A further difference was the minimal capillary and arteriolar endothelial swelling, and absence of cytoplasmic changes or lysis of surface membranes of capillary endothelial cells. Perivascular hemorrhage and interstitial edema was not present. We did find fibrin in the lung and kidney vessels of two shocked and transfused baboons which may have been from the infused blood because it had changes characteristic of degeneration and a lack of evidence of local thrombosis. It is important once again to point out differences in our experiments compared to others: our animals were intact and had all homeostatic mechanisms operational in contrast to an artificial situation involving anesthesia, mechanical ventilation, and thoracotomy and artificial perfusion force.

Summary

The effect of hemorrhagic shock and massive blood transfusion on pulmonary gas exchange was determined in unanesthetized, spontaneously breathing baboons.

After one hour at 60 mm Hg mean arterial pressure (MAP) and a second hour at 40–45 mm Hg MAP produced by hemorrhage, resuscitation back to baseline MAP was accomplished by transfusion of ACD blood which had been stored for 16–21 days. An isovolemic exchange transfusion was then carried out until twice the animal's calculated blood volume had been infused. The transfused blood was found to develop microaggregates similar in particle size and distribution to those in stored human blood.

Arterial blood gas determinations obtained within thirty minutes after completion of the transfusion indicate no dysfunction in the capability of the lung to maintain P_aO_2, P_aCO_2 and pH after a period of severe shock and massive transfusion.

No significant changes in mean systemic arterial, mean left atrial, mean pulmonary artery, or mean central venous pressures were noted. In particular, mean pulmonary arterial pressure was never elevated above 14 mm Hg during transfusion.

Light and electron microscopy findings did not demonstrate clear evidence of pulmonary microembolizations from the transfused blood.

We conclude that there is no incapacity of the lungs to maintain normal gas exchange immediately following shock and massive transfusion. From clinical and experimental data thus far published it is difficult to assess the role of transfusion following hemorrhagic shock in producing pulmonary dysfunction. Further studies are underway to determine whether hypoxemia is a late complication of shock and transfusion.

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References

1. Bennett, S. H., Geelhoed, G. W., Aaron, R. K., Solis, R. T. and Hoye, R. C.: Pulmonary Injury Resulting from Perfusion of Stored Bank Blood in the Baboon and Dog. J. Surg. Res., **13**:295, 1972.
2. Collins, J. A.: The Causes of Progressive Pulmonary Insufficiency in Surgical Patients. J. Surg. Res., **9**:685, 1969.
3. Connell, R. S. and Swank, R. L.: Pulmonary Fine Structure After Hemorrhagic Shock and Transfusion of Ageing Blood. Microcirculatory Approaches to Current Therapeutic Problems Symposia. 6th Europ. Conf. Microcirculation, Aalborg, 1970. Basel, Karger, 49, 1971.
4. Cook, W. A. and Webb, W. R.: Pulmonary Changes in Hemorrhagic Shock. Surgery, **64**:85, 1968.
5. Hedley-Whyte, J., Radford, Jr., E. P. and Laver, M. B.: Nomogram for Temperature Correction or Electrode Calibration During PO_2 Measurements. J. Appl. Physiol., **20**: 785, 1965.
6. Hisson, W. and Swank, R. L.: Screen Filtration Pressure and Pulmonary Hypertension. Am. J. Physiol., **209**:715, 1965.
7. Jennevein, E. P. and Weiss, D. L.: Platelet Microemboli Associated with Massive Blood Transfusion. Am. J. Pathol., **45**:313, 1964.
8. McLaughlin, J. S.: Physiologic Consideration of Hypoxemia in Shock and Trauma. Ann. Surg., **173**:667, 1971.
9. McNamara, J. J., Burran, E. L., Larson, E., Omiya, G., Suchiro, G. and Yamase, H.: Effect of Debris in Stored Blood on Pulmonary Microvasculature. Ann. Thorac. Surg., **14**:133, 1972.
10. McNamara, J. J., Molot, M. D. and Stremple, J. F.: Screen Filtration Pressure in Combat Casualties. Ann. Surg., **172**: 334, 1970.
11. Moseley, R. V. and Doty, D. B.: Death Associated with Multiple Pulmonary Emboli Soon After Battle Injury. Ann. Surg., **171**:336, 1970.
12. Simmons, R. L., Heisterkamp, C. A., III, Collins, J. A., Bredenberg, E. C., Mills, E. D. and Martin, A. M.: Respiratory Insufficiency in Combat Casualties: IV. Hypoxemia During Convalescence. Ann. Surg., **170**:53, 1969.
13. Simmons, R. L., Heisterkamp, III, C. A., Collins, J. A., Gerrslar, S. and Martin, A. M.: Respiratory Insufficiency in Combat Casualties: III. Arterial Hypoxemia after Wounding. Ann. Surg., **170**:45, 1969.
14. Solis, R. T. and Gibbs, M. D.: Filtration of microaggregates in Stored Blood. Transfusion, **12**:245, 1972.
15. Veith, F. J., Hagstrom, J. W. C., Panossian, A., Nehlsen, S. K. and Wilson, J. W.: Pulmonary Microcirculatory Response to Shock, Transfusion and Pump-Oxygenator Procedures: A Unified Mechanism Underlying Pulmonary Damage. Surgery, **64**:95, 1968.

Management of the Pancreas After Pancreaticoduodenectomy

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PANCREATICODUODENECTOMY IS WELL ESTABLISHED in the armamentarium of the surgeon treating periampullary carcinoma. With refinement of operative technique and more enlightened management during the postoperative period, the morbidity and mortality of this procedure have been reduced significantly.[8,15,16] Survival rates in patients with carcinoma of the head of the pancreas, although still less than desirable, are encouraging, and even more gratifying long-term results have been obtained in patients with carcinoma of the ampulla of Vater and distal common bile duct.

In recent years, a variety of methods have been advocated for management of the pancreas after pancreaticoduodenectomy. Pancreatic fistulae and recurrent tumor have stimulated efforts to modify the standard Whipple operation with its accompanying pancreaticojejunostomy.

Four major options are available to the surgeon when pancreaticoduodenectomy is indicated: 1) pancreatic duct-to-jejunal mucosa anastomosis; 2) inversion of the transected end of the pancreas into the jejunal lumen; 3) ligation of the pancreatic duct with oversewing of the transected pancreas; and 4) total pancreatectomy (Fig. 1).

To compare the merits and deficiencies of these modes of management, a retrospective review of the lengthy experience with these procedures at the UCLA Hospital was undertaken and led to the report presented herein.

Clinical Material

Sixty-five patients underwent pancreaticoduodenectomy at this institution during the 20-year period between 1951 and 1972 (Table 1). Thirty-nine had carcinoma of the head of the pancreas, 16 had carcinoma of the ampulla of Vater, and 10 had carcinoma of the distal common bile duct. Their ages ranged from 3 to 84 years; 29 patients were in their seventh or eighth decade of life. The operative mortality for the overall series was 13.8%, but this was reduced to 5.1% during the past 9 years.

Pancreatic fistulae developed in 12 patients, four of whom were among the nine operative deaths. In the other eight patients, morbidity ranged from drainage of pancreatic juice through a small sinus tract for 2 to 4 weeks to intra-abdominal abscesses that required surgical drainage.

Pancreatic Duct-to-Jejunal Mucosa Anastomosis

In ten patients continuity of the gastrointestinal tract was reconstructed by anastomosis of a large dilated pancreatic duct directly to the mucosa of the jejunum. The pancreaticojejunostomy was performed end-to-end in three patients; in seven the transected end of the pancreas was anastomosed to the side of the jejunum. In none of the patients with a dilated pancreatic duct and a direct duct-to-mucosa anastomosis did a pancreatic fistula develop. One of the patients died of superior mesenteric artery thrombosis eight days after operation. A second patient died 9 months postoperatively of recurrent tumor. Four patients died of recurrent tumor at 24 months, 29 months, 33 months, and 35 months. Four patients are still alive, two at 3 years, one at 14 months, and one 3½ months postoperatively.

Five patients with a small pancreatic duct had a duct-to-mucosa anastomosis. Their pancreatic ducts ranged from 2 to 4 mm. in diameter, and the anastomoses varied from four quadrant stitches to several stitches

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of fine suture material. Four of the anastomoses were done in an end-to-end fashion, and one was end-to-side. In the patient with the end-to-side anastomosis, a pancreatic fistula developed early in the postoperative course, and he died of hepato-renal failure one month postoperatively. Three patients survived 7½ months, 15 months, and 19 months before death from recurrent disease. One patient is alive at 3 years 9 months.

Invagination of Cut End of Pancreas into Jejunum

In 38 patients the pancreaticojejunostomy was performed end-to-end in such a way as to invaginate the cut end of the pancreas into the end of the jejunum. The anastomosis was performed between the capsule of the pancreas and the serosal surface of the jejunum with an outer layer of interrupted silk sutures and an inner row of interrupted cat-gut sutures joining the cut edge of the pancreas to the mucosa and sub-mucosa of the jejunum. A small plastic or rubber catheter generally is placed in the duct of Wirsung and either brought down the loop of jejunum and out the abdominal wall or left to lie in the jejunum to be passed spontaneously. The operative reports of 24 of the 38 patients noted such a catheter. A pancreatic fistula developed in eight patients with the invaginating type of anastomosis, seven of whom had a small polyethylene catheter placed into the duct of Wirsung and into the jejunal loop. Two of the eight patients with fistulae died 9 and 13 days postoperatively. Four of the fistulae closed after 2 to 4 weeks of drainage with three of these patients dying of recurrent tumor at 6 months. One fistula drained for 4 months, and the patient underwent four operations for intra-abdominal abscesses before dying at 7 months postoperatively. The most persistent fistula drained for 6 months before closing. The patient died 9 years postoperatively from unrelated causes. Sixteen patients who underwent the end-to-end invaginating anastomosis and did not develop fistulae died of recurrent tumor from 6 months to 120 months postoperatively. Seven patients who had this type of anastomosis without fistula are presently alive at 2½ months, 11 months, 2 years 8 months, 9 years, 10½ years, 13 years, and 15 years postoperatively.

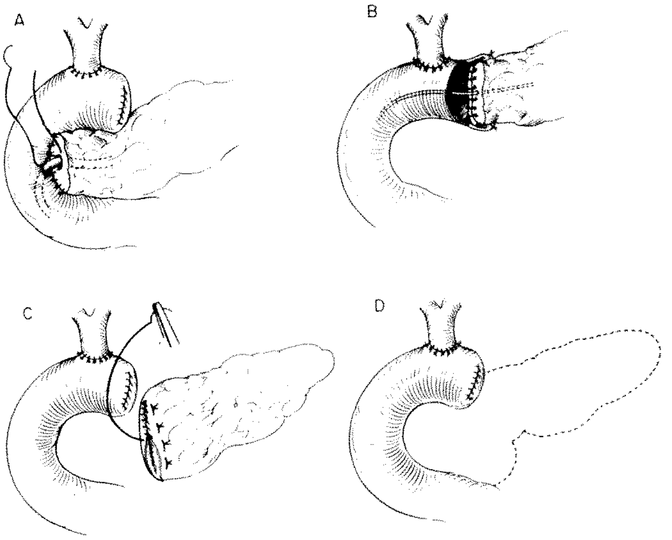

FIG. 1. Diagrammatic representation of four methods employed in the management of the pancreas when pancreaticoduodenectomy is indicated: A) anastomosis of the pancreatic duct to the mucosa of the jejunum; B) inversion of the cut end of the pancreas into the jejunum; C) ligation of the pancreatic duct with oversewing of the transected end of the pancreas; and D) total pancreatectomy.

In five patients found to have a small pancreatic duct, the transected end of the pancreas was buried into an opening made in the side of the jejunum with the bowel wall being sewn down to the pancreas in two layers. There was one pancreatic fistula among these five patients, and in one patient, a bile fistula developed from the end-to-end choledochojejunostomy. One patient died 3 weeks postoperatively of renal failure and sepsis. The other four died of recurrent tumor from 3 to 18 months postoperatively.

Ligation of Pancreatic Duct

In four patients, the pancreatic duct was ligated and the transected end of the pancreas oversewn with interrupted sutures. Pancreatic fistulae developed in two of these patients, one of whom died 23 days postoperatively. The other fistula closed spontaneously in 3 weeks, and the patient died 9 months postoperatively of recurrent

TABLE 1. *Postoperative Results in 65 Patients undergoing Pancreaticoduodenectomy*

Technique	No. Patients	Operative Deaths	Fistulae	Deaths with Recurrent Tumor	Pancreatic Insufficiency
Duct to mucosa					
Dilated duct	10	1	0	5	2
Normal duct	5	1	1	3	0
Inversion					
End-to-end	38	5	8	20	4
End-to-side	5	1	1	4	1
Ligation	4	1	2	3	—
Total Pancreatectomy	3	0	—	1	—
Total	65	9	12	36	7

tumor. One patient died of recurrent tumor 6 months after operation. The fourth patient lived 7 years 8 months before dying of recurrent tumor.

Total Pancreatectomy

In three patients the entire pancreas was removed at the time of pancreaticoduodenectomy. It is of interest that marginal ulceration developed in two of these patients at the gastrojejunostomy site during the first two postoperative weeks. One patient died 3 months postoperatively of recurrent tumor, and the other two are alive 8½ and 1½ months postoperatively.

Discussion

Pancreatic fistula formation, most often the result of breakdown of the pancreaticojejunostomy, with associated erosion, hemorrhage, and infection is the most frequent and serious complication of pancreaticoduodenectomy.[9,10,15] In our series, pancreatic fistulae were associated with four of the nine operative deaths and were the most common cause of postoperative morbidity. In our patients undergoing pancreaticoduodenectomy with partial pancreatectomy, fewer postoperative problems occurred in those who had a direct anastomosis between the pancreatic duct and the mucosa of the jejunum. This was particularly true in the ten patients who had dilated pancreatic ducts secondary to long-term obstruction, none of whom were among those with complications of postoperative fistulae. In addition to a technically easier and better anastomosis with a dilated duct from long-term obstruction, the associated chronic pancreatitis with scarring and fibrosis of the pancreatic capsule renders this anastomosis more secure than one performed in a patient with a normal pancreas. It is of interest that six of these ten patients survived from 2½ to 3 years after operation. The one pancreaticojejunostomy fistula occurring among the patients with a direct duct-to-jejunal mucosa anastomosis was in a patient with a small pancreatic duct sewn with fine suture material to the side of the jejunum.

The end-to-end invaginating type of anastomosis was performed in 58% of our patients undergoing pancreaticoduodenectomy. Eight of the 12 pancreatic fistulae occurred in these patients. The rather tenuous status of suturing to the pancreatic capsule is well recognized. Without an anastomosis of the pancreatic duct to the jejunal mucosa, development of a leak at the anastomotic site is more likely to occur and may be further aggravated by the digestion of pancreatic enzymes. Studies of pancreatic ductal operations have, in general, indicated a superiority of duct-to-mucosa anastomosis when compared to implantation of the transected pancreas in terms of functional results and patency of the pancreatic duct.[1,4]

Brunschwig,[2] Goldsmith *et al.*[6] and Rabwin and Karlin[12] are opponents of pancreaticojejunostomy for several reasons: 1) It is an added and time-consuming step that sets up the potential fistula. 2) When the pancreatic duct is ligated and the stump of the pancreas oversewn, a fistula, should it develop, is less severe and devastating and the pancreatic drainage often clear and less erosive. Pancreatic secretions that leak from a pancreaticojejunostomy appear to be activated by biliary and enteric enzymes and infection with resulting digestion of surrounding tissues. 3) The lack of external pancreatic secretions after ligation of the pancreatic duct or total pancreatectomy can be controlled quite well with oral pancreatic enzymes. 4) When a pancreaticojejunostomy is performed, some question exists as to the continued patency of the pancreatic duct.

Fish *et al.*[5] pointed out that when the duct remains patent, it is rather surprising that pancreatic insufficiency should develop in any patient after pancreaticoduodenectomy since only 10% of the gland is necessary for exocrine function, and most patients retain at least 50% of their gland. In our series, 31 patients survived more than one year postoperatively. Seven of these patients had symptoms and signs of pancreatic insufficiency, twenty-one were normal, and three could not be evaluated. Two of the seven patients with pancreatic insufficiency had a duct-to-mucosa anastomosis, four had an end-to-end invaginating type anastomosis, and one had the transected end of the pancreas buried into the side of the jejunum. The patient in our series who lived 7 years 8 months after ligation of the pancreatic duct was well-controlled on pancreatic enzymes.

We have been impressed by the rather variable nature of pancreatic exocrine replacement required for long-term survivors after pancreaticoduodenectomy. The following case reports illustrate this marked variability.

Case Reports

Case 1: A 46-year-old female was referred to the UCLA Hospital in August 1961, at which time she underwent vagotomy, pyloroplasty, gastrojejunostomy, and gastrostomy for ulcerated diverticulae in the second and third portions of the duodenum. One month later she was reoperated upon for a perforated marginal ulcer at the site of the gastrojejunostomy. She was explored in November 1961 for complete obstruction of the third portion of the duodenum, and pancreaticoduodenectomy was performed for a carcinoma of the head of the pancreas. She did well for five years, but in October 1966 she required still another operation for a marginal ulcer. Further gastric resection and repeat vagotomy were performed; there was no evidence of metastatic disease at this time. Four years later in January 1970, the patient underwent exploratory laparotomy for a rapidly enlarging liver found to be secondary to large tumor nodules. Biopsy revealed suspected islet cell carcinoma metastatic from the head of the pancreas. Subsequent serum gastrin levels were significantly elevated. In July 1970, the patient underwent total gastrectomy. In mobilizing a jejunal limb to reach the esophagus, the blood supply was injured to the proximal jejunal limb that had been anastomosed to the common bile duct 9 years earlier. When the pancreaticojejunostomy was taken down, complete stenosis of the pancreatic duct was found at the site of anastomosis. There was no route whereby pancreatic exocrine secretion could enter the alimentary tract. Although the patient had never taken pancreatic enzymes, she had not had symptoms of pancreatic exocrine insufficiency.

Case 2: A 38-year-old male ex-soldier came to UCLA from Vietnam four months after undergoing a Whipple procedure for a mass in the head of the pancreas discovered during operation for a gangrenous gallbladder secondary to salmonellosis. The pancreatic duct had been ligated and the stump of the pancreas oversewn. Histologic examination of the pancreatic specimen disclosed chronic pancreatitis. Examination at UCLA revealed a left upper quadrant pancreatic fistula. He had not taken pancreatic enzymes at any time since the pancreaticoduodenectomy. He reported having two or three firm, greasy, foul-smelling bowel movements per day. Viokase was begun, and the patient was followed closely. The fistula closed after three months. There was no significant change in the nature or number of bowel movements on the Viokase. Sixteen months later the patient was operated upon for obstructive jaundice found to be due to a small calculus in the common bile duct blocking the choledochojejunostomy. The site of the previous pancreatic fistula was found at the oversewn end of the pancreas. The stump of the pancreas was cut back, the pancreatic duct located, and a pancreaticojejunostomy was performed. The choledochojejunostomy was revised. Postoperatively, pancreatic enzymes were not given. The patient's stool and bile habits were unchanged from their preoperative status. Six months later RATO Test was compatible with pancreatic insufficiency, but the patient was not on medication, had gained weight, felt well, and was working 8 hours per day. His stools and bowel habits were not significantly different than when he was first seen.

Of particular interest is the first patient above who had no pathway whereby pancreatic exocrine secretions could enter the alimentary tract yet had no symptoms of pancreatic insufficiency.

Ligation of the pancreatic duct and oversewing of the transected end of the pancreatic remnant have been utilized to reduce the length of the operative procedure and to eliminate the troublesome pancreaticojejunostomy. In a recent interesting report, Goldsmith and co-workers[6] compared a group of 34 patients who had undergone reimplantation of the pancreatic duct into the gastrointestinal tract with a group of 45 patients who had their pancreatic ducts ligated at the time of pancreaticoduodenectomy. Postoperative morbidity and mortality rates were similar between the two groups. They found that the need for pancreatic endocrine and exocrine supplementation in both groups appeared to be the same, the dosage and length of medication time being variable. At autopsy, patients in both groups showed scarring of the pancreas, stenosis of the proximal portion of the pancreatic duct, and dilatation of the remaining pancreatic duct. Histological sections showed no significant difference between the two groups in terms of exocrine function as reflected in acinar cell structure nor was there any difference in endocrine function as reflected by the islands of Langerhans. Pancreatic fistulae developed in 27% of their patients who had the pancreatic duct anastomosed and in 22% of those who had undergone ligation of the duct. Although the rate of fistula formation in our four patients was 50% after oversewing of the transected end of the pancreas, use of the procedure would seem to be indicated in carefully selected patients.

In recent years, enthusiasm has been expressed for performance of total pancreaticoduodenectomy in the treatment of some periampullary carcinomas.[7,12,13] The high operative morbidity and mortality associated with total pancreatectomy when it was first advocated by Ross[14] have now been reduced to more acceptable levels. Operative mortality rates for this procedure have been reported to be as low as 9%.[7] Certainly this is within the range of operative mortality reported in most series for partial pancreaticoduodenectomy. Besides removing the often critical pancreaticojejunostomy anastomosis, total pancreatectomy prevents cancer from being left at the line of resection of the pancreas, reduces the incidence of residual tumor in peripancreatic nodes, removes the possibility of new tumor developing from multicentric sites in the remaining pancreas, and prevents implantation and growth of tumor cells present in the ductal system at the time of operation.[3,7,12]

ReMine *et al.*[13] pointed out that chance for cure is not lost when regional lymph nodes are involved with tumor. They suggest that a more thorough job of *en masse* removal of areas of lymphatic drainage can be accomplished when total pancreatectomy is performed.

Collins *et al.*[3] reviewed 11 consecutive Whipple operations performed in their hospital and found that seven patients had lymphatic or nodal invasion of tumor, four had invasion of peripancreatic tissues, five had tumor present at or distal to the line of resection, and one patient had carcinoma *in situ* in areas of the pancreas distal to the primary tumor.

Hicks and Brooks[7] recently reported on 11 patients who underwent total pancreatectomy between 1964 and 1970 and compared them with the 11 patients reported by Collins *et al.*[3] who had partial pancreatectomy in the same hospital between 1956 and 1964. The total pancreatectomy patients had a lower operative mortality rate (9.1% vs. 18.2%), fewer postoperative complications, and a longer average postoperative survival time. Whether the better results obtained in this group were related to the actual procedure or to the fact that the patients were operated upon during the most recent 6 years is speculative.

Pathologic examination of the specimens from the 11 patients who had total pancreatectomy revealed "tumor cells at or distal to the usual Whipple line" in four. It has been documented that the surgeon cannot determine grossly small areas of remaining tumor at the line of resection.[7,11] Likewise, frozen section specimens cannot exclude remaining small areas of neoplasm. ReMine and co-workers[13] support the idea that the high incidence of "recurrence of tumor" and a large percentage of late deaths after a Whipple procedure probably are secondary to persistence of the primary tumor. Forty-one of our 54 patients who survived the pancreaticoduodenectomy were dead at the time of this report; thirty-six died with recurrent tumor. Autopsy reports were obtained on fourteen, with recurrent carcinoma of the pancreatic remnant being reported in only three patients. This suggests that in our series total pancreatectomy would not have increased significantly the long-term survival rates. Eight of the fourteen patients had liver metastases, and five had obstruction of the choledochojejunostomy by recurrent tumor. Most patients had multiple intra-abdominal metastases involving small bowel serosa, colon, peritoneum, omentum, adrenals, ovaries, or kidneys. One patient had obstruction of the portal vein and inferior vena cava by tumor. Four had pulmonary metastases, and three others had metastases to the pleura without lung involvement.

As noted above, pancreatic exocrine insufficiency does occur in some patients who have had a partial pancreatectomy and gastrointestinal continuity reconstructed by pancreaticojejunostomy. Objections to total pancreatectomy or to ligation of the pancreatic duct on the basis of pancreatic exocrine or endocrine insufficiency are valid but cannot be accepted as reasons for abandoning totally the use of the procedures.[2,9,12,13] In patients with either ligation of the pancreatic duct or total pancreatectomy, pancreatic exocrine function usually may be controlled satisfactorily with one of the commercially available pancreatic extracts (Pancreatin) or whole pancreas preparations (Viokase). We have used Viokase most often because of its more complete hydrolysis of proteins. With dietary and enzymatic regimens, we have been able to control steatorrhea in most of our patients with pancreatic insufficiency.

In patients who have had total pancreatectomy, the pancreatic endocrine function also must be controlled. In general, insulin requirements vary from 15 to 50 units of insulin per day, but the dosage requirements generally stabilize in most patients after a few weeks. Although the diabetes in some patients may be quite brittle, it usually is managed without great difficulty. It is interesting to note that when a patient has been rather stable on a particular insulin dose, an increasing or decreasing need for insulin usually indicates recurrent tumor.[7,12]

Our experience with total pancreatectomy for carcinoma of the head of the pancreas has been limited; nevertheless, we feel that this procedure may have certain advantages in carefully selected patients. For instance, patients with multiple tumor nodules or a mass in the head of the pancreas with marked induration of the pancreas distally in such a way as to prevent localization of the tumor may be candidates for total pancreatectomy. Whether long-term results will justify this extended operation in patients with more localized lesions remains to be seen. Further evaluation would seem indicated.

Summary

Management of the pancreas at the time of pancreaticoduodenectomy must necessarily vary with each patient. When there is a large dilated pancreatic duct and a good duct-to-mucosa anastomosis can be obtained with the jejunum, this type of reconstruction of the alimentary tract with accompanying choledochojejunostomy and gastrojejunostomy is most desirable. A relatively normally functioning gastrointestinal tract should then be present 3 to 4 months postoperatively. The results of the invaginating type of anastomosis have been less satisfactory with the development of hazardous fistulae and evidence that the cut end of the duct closes in some patients. Our experience with ligation of the pancreatic duct and total pancreatectomy has been limited. Ligation of the duct shortens the operative procedure, and, should a fistula develop, it drains pure pancreatic juice rather than biliary-pancreatic intestinal juices and is less irritating.

Total pancreatectomy may be considered in those patients suspected of having multicentric tumor or patients in whom the changes of chronic pancreatitis cannot be distinguished from neoplastic involvement and the indicated limits of the resection clearly defined.

Control of exocrine function may present a problem regardless of the treatment of the pancreatic remnant, but the degree of deficiency is difficult to predict. Total pancreatectomy adds the concerns of permanent diabetic management to the postoperative care, and although most patients are controlled without undue difficulty, others will require careful prolonged management.

References

1. Bonta, J. A.: An Experimental Study of Retrograde Pancreatojejunostomy. Surg. Forum, 5:408, 1954.
2. Brunschwig, A.: Discussion of a Report upon a Technique for Pancreatoduodenectomy. Surg. Gynecol. Obstet., 118:263, 1964.
3. Collins, J. J., Craighead, J. E. and Brooks, J. R.: Rationale for Total Pancreatectomy for Carcinoma of the Pancreatic Head. New. Engl. J. Med., 274:599, 1966.
4. Ferguson, D. J. and Wangenstern, O. H.: Experimental Anastomosis of the Pancreatic Duct. Ann. Surg., 132:1066, 1950.

5. Fish, J. C., Smith, L. B. and Williams, R. D.: Digestive Function after Radical Pancreatoduodenectomy. Amer. J. Surg., **117**:40, 1969.

6. Goldsmith, H. S., Ghosh, B. C. and Huvos, A. G.: Ligation versus Implantation of the Pancreatic Duct after Pancreatoduodenectomy. Surg. Gynecol. Obstet., **132**:87, 1971.

7. Hicks, R. E. and Brooks, J. R.: The Total Pancreatectomy for Ductal Carcinoma. Surg. Gynecol. Obstet., **133**:16, 1971.

8. Howard, J. M.: Pancreatoduodenectomy: Forty-One Consecutive Whipple Resections without an Operative Mortality. Ann. Surg., **168**:629, 1968.

9. Lansing, P. B., Blalock, J. B. and Ochsner, J. L.: Pancreatoduodenectomy: A Retrospective Review 1949 to 1969. Amer. Surg., **38**:79, 1972.

10. Monge, J. J., Judd, E. S. and Gage, R. D.: Radical Pancreatoduodenectomy: A 22-Year Experience with the Complications, Mortality Rate and Survival Rate. Ann. Surg., **160**: 711, 1964.

11. Porter, M. R.: Carcinoma of the Pancreatico-Duodenal Area—Operability and Choice of Procedure. Ann. Surg., **148**: 711, 1958.

12. Rabwin, M. H. and Karlan, M. S.: Partial and Total Pancreatectomy for Periampullary Carcinoma. Calif. Med., **104**: 437, 1966.

13. ReMine, W. H., Priestley, J. T., Judd, E. S. and King, J. N.: Total Pancreatectomy. Ann. Surg., **172**:595, 1970.

14. Ross, D. E.: Cancer of Pancreas: Plea for Total Pancreatectomy. Amer. J. Surg., **87**:20, 1954.

15. Sato, T., Saitoh, Y., Koyama, K. and Watanabe, K.: Preoperative Determination of Operability in Carcinoma of the Pancreas and the Periampullary Region. Ann. Surg., **168**:876, 1968.

16. Warren, K. W., Veidenheimer, M. C. and Pratt, H. S.: Pancreatoduodenectomy for Periampullary Cancer. Surg. Clin. N. Amer., **47**:639, 1967.

The Variable Significance of Condylomata Acuminata

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CONDYLOMATA ACUMINTA, or venereal warts, are lesions which ordinarily can be diagnosed by their gross warty appearance and effectively treated either with podophyllin or by cautery. Occasionally, however, a condylomatous lesion may suggest the possibility of a malignant growth by its clinical appearance or may be found to harbor a malignancy on histologic examination.

We recently have encountered three cases of unusual condylomata which prompted us to review the literature on this subject and to report our cases.

Case Reports

Case 1. A 36-year-old man was admitted January 1, 1972, for removal of multiple large condylomata involving the skin of the penis, the scrotum and the perineum, including coccygeal, gluteal, and both inguinal regions. The largest lesion measured 11.5 cm., × 8.5 cm. (Fig. 1). The patient stated that similar lesions had been treated successfully with podophyllin ten years previously. Three years prior to admission the lesions recurred, and attempted treatment with podophyllin was unsuccessful. During the month prior to admission the lesions began to enlarge and spread.

Two days following admission the lesions were excised with cautery. Because of the depth of the lesions, it was not possible to preserve any skin beneath the lesions (Fig. 2). On January 19, 1972, the larger wounds were covered with split thickness grafts, and the smaller wounds were closed secondarily.

When the patient was seen in the surgery clinic (Fig. 3) on March 2, 1972, two recurrences were noted, one on the penis and one in the perianal region. These were thoroughly cauterized The patient was last seen on April 7, 1972, at which time no recurrences were noted.

Histologic examination of the excised lesions revealed typical condylomata acuminata.

Case 2. A 38-year-old white woman was admitted September 22, 1971, for removal of multiple perianal condylomata measuring up to 1.5 cm. in diameter. Sigmoidoscopy to 17 cm., revealed no mucosal abnormalities. The day following admission the larger lesions were excised, and the smaller ones were fulgurated.

Histologic examination of the lesions was interpreted as condylomata acuminata with a focus of baseloid carcinoma.

Case 3. A 53-year-old white man was admitted January 9, 1972, for removal of a 4.7 cm. × 2.5 cm. condylomatous lesion of the posterior perianal area. History revealed the lesion had been present for several years and had been enlarging during the month prior to admission. The referring physician had treated the lesion with podophyllin without success. The day following admission the lesion was excised.

Histologic examination of the excised specimen showed carcinoma *in situ* and a questionably invasive squamous cell carcinoma arising in condylomata acuminata.

Discussion

Condylomata acuminata are thought to be caused by an auto-inoculable, filtrable virus similar or identical to the virus of verruca vulgaris and verruca plana.[2,8,9] They tend to occur in moist, warm areas of the body and are frequently associated with a discharge. Frequently they are associated with poor hygiene.

Carcinoma arising within a condyloma is known to occur. Rhatigan, *et al.*[16] described six patients with condylomata of the penis who eventually were found to harbor squamous cell carcinomas. Four of the carcinomas arose in condylomata acuminata and two in giant condylomata. Two cases of squamous cell carcinoma arising in perianal condylomata have been reported,[7,19] as well as a metastatic squamous cell carcinoma arising in a giant condyloma of the inguinal area.[15] Four cases of carcinoma arising in condylomata of the anal canal recently have been reported by Sawyers.[18] No case of

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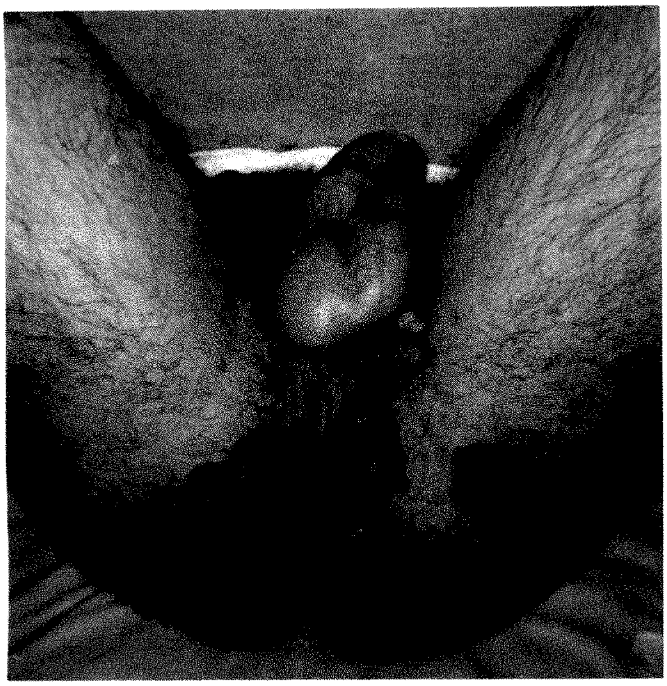

FIG. 1. Preoperative photograph of patient No. 1 on January 2, 1972.

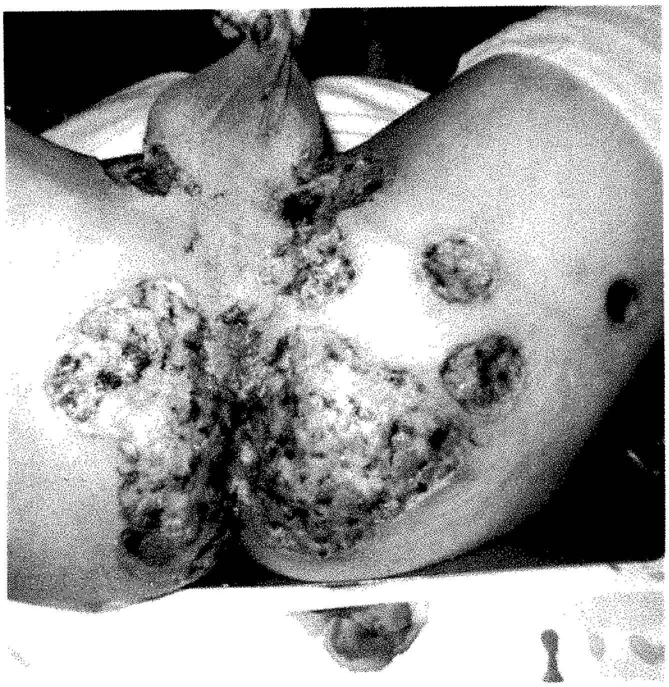

FIG. 2. Photographs of patient No. 1 after excision of condylomata and before application of skin grafts, January 19, 1972.

a carcinoma arising in a condylomata previously has been reported in a female.

Giant condylomata are clinically malignant variants of condylomata acuminata. The first two cases of this unusual lesion were reported by Buschke[14] in 1896 in Neisser's Stereoscopic Atlas. Buschke referred to the lesion as a "pointed condyloma" of the penis. In 1932, he added a third case of the same lesion.[3] Lowenstein later described the characteristics of this peculiar type of condyloma, thereafter known variously as the Buschke-Lowenstein tumor, giant condyloma, and carcinoma-like condyloma. He described the lesion as being histologically identical to simple condylomata with the exception that the lesion destroyed underlying tissues. He attributed this destruction to displacement rather than actual invasion by the lesion.

All of Buschke's and Lowenstein's cases involved only the penis. Since then numerous cases of this tumor involving the penis have been reported, most of which required penectomy to control the growth of the tumor.[1,4,5,6,8,13,15] Only four cases of giant condylomata involving areas other than the penis have been reported, one perianal,[5] one inguinal,[15] one rectal,[12] and one involving the vulva and the rectum,[10] which is the only previously reported case of giant condylomata in a female. The first two patients subsequently developed squamous cell carcinoma. The carcinoma of the inguinal lesion developed lymph node metastases.

The most dramatic demonstration of the giant condylomata in the literature appeared in the excellent paper by Dawson, *et al.*[5] They reported a case of giant condylomata arising in a perianal location that eventually required a pelvic exenteration to control the growth of the lesion.

Kaplan[11] reported the first successful treatment of

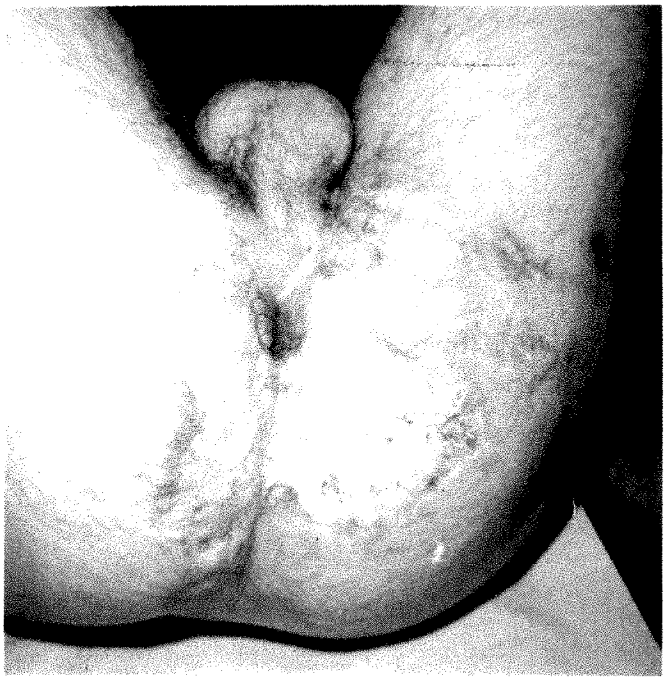

FIG. 3. Postoperative photograph of patient No. 1, March 2, 1972.

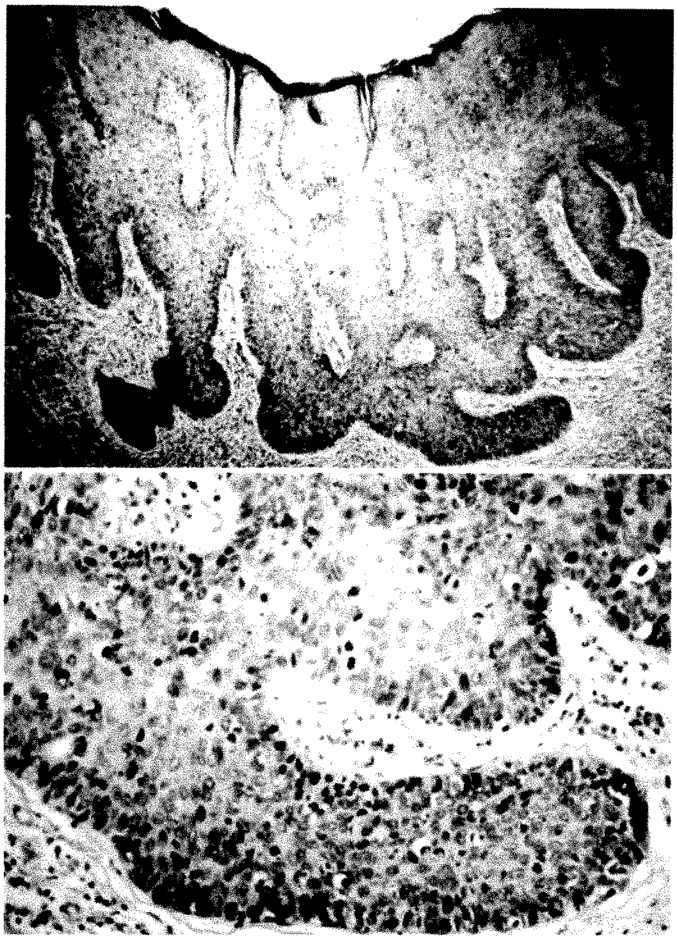

FIG. 4 A and B. Photomicrographs of excised lesion from Case 2 showing focus of baseloid carcinoma in condyloma. Original magnifications approximately 35X (A) and 120X (B).

condylomata acuminata with podophyllin, a resin from the mandrake or May apple, a plant indigenous to a large part of the United States. The reported effects of podophyllin are to incite mitotic activity in the prickle cell layer of the lesion and to arrest mitosis at the same time.[17] In addition, podophyllin causes cellular swelling and increased nuclear pyknosis which, with the increased mitotic activity caused by this agent, can make the differentiation of podophyllin-treated condylomatous lesions from carcinoma difficult.[15] The Buschke-Lowenstein tumor, or giant condyloma, is notably resistant to podophyllin.[12]

The only effective therapy for giant condylomata is surgical excision or fulguration.[6,8] Lesser forms of therapy are fraught with failure and recurrence. Even when completely excised, the tumor frequently will recur, and radical surgery has at times been necessary to control the tumor.

The diagnosis of giant condylomata is made clinically by observing the ability of the tumor to grow, recur, destroy tissue, and occasionally to pursue a metastatic course.

Carcinoma arising in condylomata acuminata or giant condylomata can be detected only by biopsy and histologic examination. Biopsy is indicated when any suspicion of carcinoma is present. Frequently the presence of carcinoma is revealed only by the pathology report after excisional biopsy. Even after biopsy, histologic differentiation of podophyllin-treated condylomata from carcinoma may be difficult if not impossible because of the cytologic changes induced by this agent. Treatment of the lesion should be governed by the location of the lesion and its histologic appearance.

Summary

One case of large benign condylomata acuminata and two cases of carcinoma arising in perianal condylomata acuminata are presented. One of the carcinomas occurred in a female and to our knowledge is the only reported case of carcinoma arising in condylomata in a female. The diagnosis of condylomata acuminata is based on its

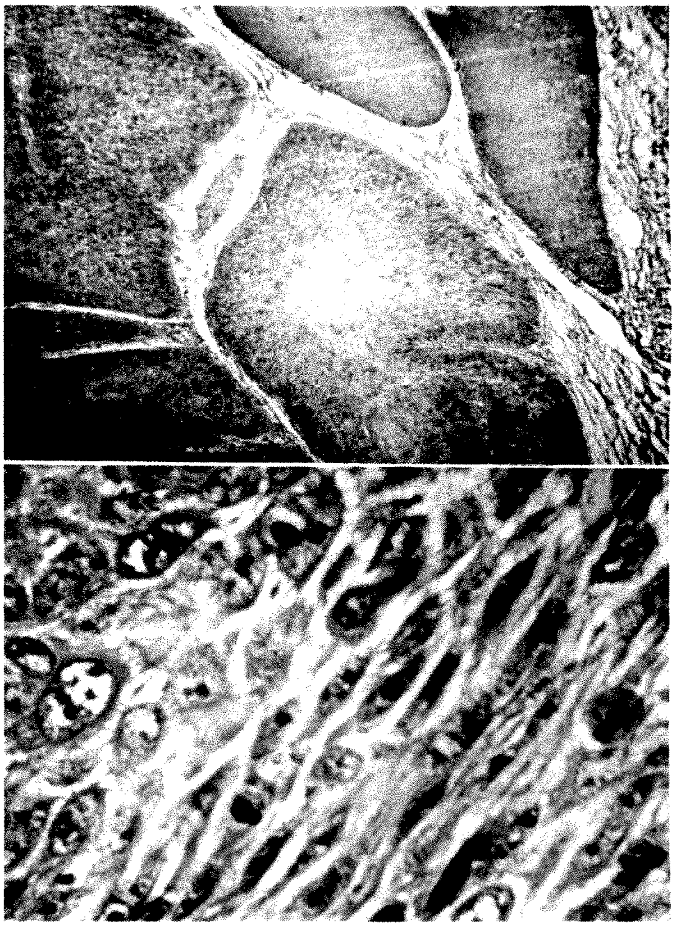

FIG. 5 A and B. Photomicrographs of excised lesion from Case 3 showing squamous cell carcinoma arising in condyloma. Original magnifications approximately 35X (A) and 400X (B).

warty gross appearance and benign clinical course. It is easily treated with either cautery or podophyllin. The diagnosis of giant condylomata is based on its ability to destroy underlying tissue and pursue a clinically malignant course. Excision is the only effective treatment, and at times excision may have to be radical to control the tumor. Carcinoma arising in condylomata acuminata or giant condylomata can be detected only by biopsy and histologic examination. Treatment will depend on the location of the lesion and its histologic appearance. Whenever a condyloma is atypical in appearance, excisional biopsy and histologic examination should be the first choice of therapy because applications of podophyllin may cause a benign condyloma to appear histologically malignant, and fulguration may alter the histology of the tissue to the extent that it can not be interpreted.

Acknowledgement

We would like to express our appreciation and thanks to Jasper L. Phillips, Jr., M. D. for his translation from the German of the article by Buschke and Lowenstein and to Henry H. Nicholson, Jr., M. D., for permission to report Cases No. 2 and 3.

References

1. Bulkley, G., Wendell, R. and Grayhack, Jr.: Buschke-Lowenstein Tumor of the Penis. J. Urol, **97**:731, 1967.
2. Burns, E. and Thompson, I.: Infections. *In* Urology. M. F. Campbell and J. H. Harrison, editors. Philadelphia, W. B. Saunders Co., Vol. 1, 527, 1970.
3. Buschke, A. and Lowenstein, L.: Uber die Beziehungen von spitzen Kondylomen zu Karzinomen des Penis, Dtsch. Med. Wochenschr. **58**:809, 1932.
4. Davies, S.: Giant Condyloma Acuminata: Incidence Among Cases Diagnosed as Carcinoma of the Penis. J. Clin. Path., **18**:142, 1965.
5. Dawson, D., Duckworth, J., Bernhardt, H. and Young, J.: Giant Condyloma and Verrucous Carcinoma of the Genital Area. Arch. Path., **79**:225, 1965.
6. Dryefuss, W. and Neville, W.: Buschke-Lowenstein Tumors (Giant Condyloma Acuminata). Am. J. Surg., **90**:146, 1955.
7. Friedberg, M. and Serlin, O.: Condyloma Acuminatum: Its Association with Malignancy. Dis. Colon Rectum, **6**:352, 1963.
8. Gersh, I.: Giant Condylomata Acuminata (Carcinoma-Like Condylomata or Buschke-Lowenstein Tumor of Penis). J. Urol., **69**:1964, 1953.
9. Goldschmidt, H. and Kligman, A.: Experimental Inoculation of Humans with Ectodermotropic Viruses. J. Invest, Dermatol., **31**:175, 1958.
10. Judge, J.: Giant Condyloma Acuminatum Involving Vulva and Rectum. Arch. Path., **88**:46, 1969.
11. Kaplan, I. W.: Condylomata Acuminata. New Orleans M. & S. J., **94**:388, 1942.
12. Knoblich, R. and Failing J.: Giant Condyloma Acuminatum (Buschke-Lowenstein Tumor) of the Rectum. Am. J. Clin. Path., **48**:380, 1967.
13. Lepow, H. and Leffler, N.: Giant Condylomata Acuminata (Buschke-Lowenstein Tumor): Report of Two Cases. J. Urol., **83**:853, 1960.
14. Lowenstein, L.: Carcinoma-Like Condylomata Acuminata of the Penis. Surg. Clin. N. Am., **23**:789, 1939.
15. Machacek, G. and Weakly, D.: Giant Condylomata Acuminata of Buschke and Lowenstein. Arch. Dermatol., **82**:41, 1960.
16. Rhatigan, R., Jimenez, S. and Shopskie, E. Condyloma Acuminatum and Carcinoma of the Penis. South. Med. J., **65**: 423, 1972.
17. Saphir, O., Leventhal, M. and Kline, T.: Podophyllin Induced Dysplasia of the Cervix Uteri (Its Histologic Resemblance to Carcinoma in Situ). Am. J. Clin. Path., **32**:446, 1959.
18. Sawyers, J. L.: Squamous Cell Cancer of the Anus and Perianus. Surg. Clin. N. Am., **52**:935, 1972.
19. Siegel, A.: Malignant Transformation of Condyloma Acuminatum (Review of the Literature and Report of a Case). Am. J. Surg., **103**:613, 1962.

Hemodynamic Observations of Adynamic Ileus in the Conscious Dog

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THE MANAGEMENT OF ADYNAMIC ILEUS, which is observed after extensive intra-abdominal surgical manipulations or which occurs in the course of diffuse peritonitis, remains a major surgical problem. Insofar as the etiology of adynamic ileus is concerned, most observers believe that the condition is due to hyperactive sympathetic influences. It has been repeatedly demonstrated, both experimentally and clinically, that interruption of sympathetic impulses by splanchnic blockage[3,26] or spinal anesthesia[17,21] restores the ability of the intestinal musculature to contract after it has been in a state of ileus. There is little doubt that one effect of splanchnic nerve stimulation is vasoconstriction of the intestinal vessels.[8] Consequently, it is possible that intestinal vascular resistance may increase and intestinal blood flow may be reduced. In addition, reduction of intestinal motility may also affect blood flow.[22] It is not obvious, however, that these hemodynamic changes actually occur during peritonitis or surgical manipulations.

In order to determine the effects of adynamic ileus on mesenteric vasoactivity and to further clarify the mechanism involved, mesenteric blood flow, mesenteric arterial vascular resistance, portal pressure and systemic arterial pressure as well as intestinal motility were studied during the course of acute peritonitis in the conscious dog.

Method

Ten mongrel dogs, weighing 20–30 kg were prepared for sterile operation after injection of intravenous sodium thiopental (30/mg/kg). The abdomen was entered through a midline incision and splenectomy was performed. The portal vein was cannulated via the splenic vein. A magnetic flowmeter probe was implanted near the origin of the superior mesenteric artery. A serosal electrode was implanted in the wall of the ileum about 30 cm proximal to the ileo-cecal valve, and a balloon was inserted from a small proximal ileostomy and advanced down near the level of the serosal electrode. After these procedures, the abdomen was closed in layers and a catheter was placed in the femoral artery. The catheter, the electrode, and the flow probe connector were covered over by a layer of skin.

Three days later a small portion of the abdominal incision was re-opened aseptically under local anesthesia and the appendix was withdrawn from the abdominal cavity. The mesenteric attachments and the appendiceal vessels were divided and ligated with silk. The base of the appendix was tightly ligated with umbilical tape. The appendix was then replaced and the abdominal cavity closed.[18]

Motor activity of the ileum, and aortic and portal pressures were recorded with calibrated pressure transducers connected to a Sanborn 760 series recording system. Electrical activity of the ileum was obtained from the serosal electrode connected to a Sanborn 760 series EKG amplifier. Reference electrodes were placed on the inner aspect of the thigh. Superior mesenteric arterial flow was monitored with a flow transducer connected to BL-610 Pulsed-Logic Flowmeter (Biotronex Laboratory, Inc.) which, in turn, was connected to a Sanborn 760 series preamplifier and recording system. Zero-flow levels were obtained by injecting 3 mg acetylcholine intravenously to produce transient cardiac arrest.[14] Intestinal vascular resistance was calculated from the pressure gradient across the gut (arterial minus portal pressure) di-

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TABLE 1. *Survival Time of Animals*

Hours after Ligation of Appendix	Number of Animals
0–12	1
12–24	6
24–48	2
48–72	1

vided by the blood flow. Resistance was expressed in millimeters of mercury per milliliter of blood flow per minute (peripheral resistance units, PRU). These recordings were obtained before and every consecutive three hour period after appendiceal ligation.

The animals received nothing by mouth, but 20 ml per kg of body weight of a solution containing 2.5% glucose and 0.45% saline was given intravenously immediately after operation and every twenty-four hours until death. No antibiotics were given to the animals preoperatively or postoperatively.

Results

The survival time of the present series of experiments is shown in Table 1. The shortest survival was 6 hours after appendiceal ligation. Six animals died between 12 and 24 hours. Three survived more than 24 hours and the longest survival was 55 hours.

Data from eight animals were analyzed for the 12 hour period following appendiceal ligation. The shortest and the longest survivals were discarded from the experiments, because the information obtained was incomplete. Figure 1 and Tables 2 and 3 indicate the status of ileal motility before and after ligation of the appendix. Slow wave activity was not impaired during the course of acute peritonitis. Spike activity, however, was significantly diminished from the third hour after ligation. On the other hand, mechanical activity was not greatly diminished until the third hour. Inhibition of motility began 6 hours after ligation and adynamic ileus was established during the subsequent 3 hours. Macroscopic necrosis of the appendix was observed beginning after 6 hours. Fluid accumulation in the intestinal lumen and ascites were also noted after 6 hours (Fig. 2).

The hemodynamic changes are summarized in Figs. 3 and 4. The mean aortic blood pressure increased to 20% above its control level within 3 hours after ligation. At the sixth hour, it was almost the same as the control and then gradually decreased to 72% of the control value at the end of twelve hours. An increase in the mean portal pressure was also noted from the third to ninth hour. These changes are not statistically significant because of individual variations of animals. The control value of the superior mesenteric artery flow (mean) was 11.5 (±.50 S.E.) ml/min/kg. This flow was increased significantly ($p < .05$) to 13.8 (±.72 S.E.) ml/min/kg three hours after ligation. However, it returned to near the control value (10.7 ± .55 S.E. ml/min/kg) at the sixth hour and then decreased significantly each consecutive three hours to 8.5 (±.75 S.E.) and 6.1 (±1.13 S.E.) ml/min/kg ($p < .01$, $p < .005$ respectively). The control value of mean superior mesenteric artery resistance was .53 (±.053 S.E.) PRU. A decrease in superior mesenteric artery resistance (12%) to .47 (±.039) PRU was observed following three hours after appendix ligation. It returned

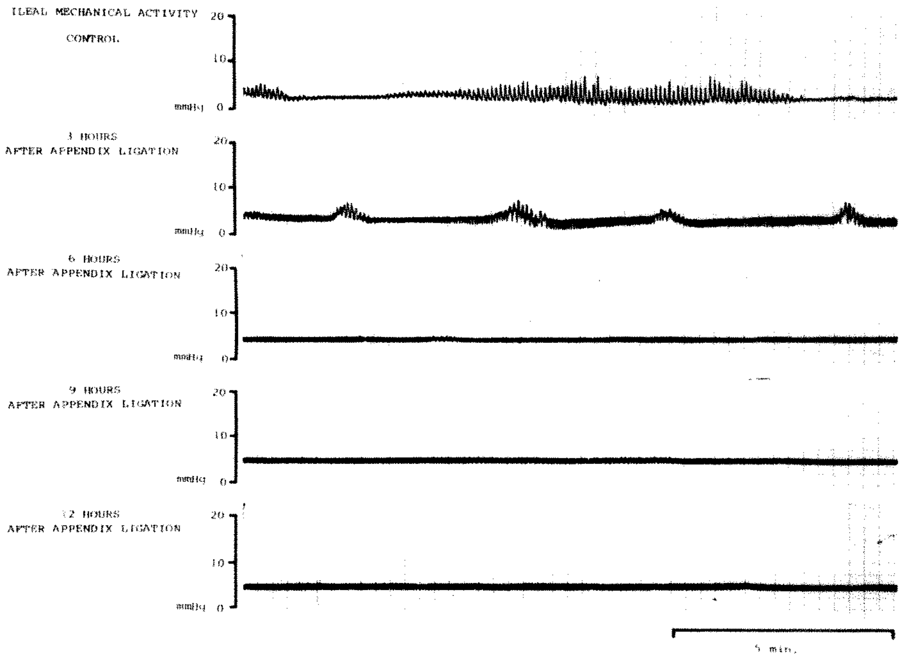

FIG. 1. Mechanical activity of the ileum before and after appendiceal ligation (Dog AL-15). Adynamic ileus was established within 6 hours after the procedure.

TABLE 2. *Electrical Activity of the Ileum*

Hours After Appendiceal Ligation	Slow Wave Activity			Spike Activity	
	Freq. (c/s)	Amp. (mV)	Slow Waves with spikes (%)	Max. Amp. (mV)	No. of Spikes in a burst
Control	10.8 ± .27	1.1 ± .08	81 ± 6.0	.48 ± .051	2.3 ± .17
3	11.0 ± .25	1.1 ± .07	42 ± 7.4**	.21 ± .071*	1.2 ± .23*
6	10.7 ± .45	1.0 ± .07	6 ± 5.8**	.01 ± .041**	.1 ± .11**
9	10.6 ± .30	.9 ± .07	0 ± .0**	.00 ± .000**	.0 ± .00**
12	10.6 ± .49	.9 ± .06	0 ± .0**	.00 ± .000**	.0 ± .00**

* Significant with $p < .01$ as compared to control value
** Significant with $p < .005$ as compared to control value
Values represent mean ± standard error of eight animals

to the control value after six hours. There was a slight increase in this resistance at the ninth and twelfth hours, .55 (±.031 S.E.), and .59 (±.056 S.E.) PRU respectively. These changes in resistance were not statistically significant. Recordings from a typical experiment (Dog AL-18) of this series appears in Figures 5–9.

Autopsy confirmed necrosis of the appendix and widespread peritonitis in each instance.

Discussion

Results of the present study suggest that in the course of acute peritonitis due to ligation of the appendix, there are four stages which can be defined in terms of the predominant condition of intestinal motility and splanchnic hemodynamics. They are the initial response to injury, the stage of inflammation, of adynamic ileus, and finally of peripheral vascular collapse. The stage of adynamic ileus began about six hours after ligation of the appendix, and was followed by the hypotensive stage. A process which was predominately inflammatory was observed before ileus became established and was similar to that observed by Nishijuma[20] who reported that acute peritonitis induced by perforation of the small intestinal wall produced a vigorous discharge of spike potentials for approximately five hours followed by paralysis and disappearance of spike potentials.

Little information is available on the hemodynamic changes associated with adynamic ileus. Most of the hemodynamic studies have been performed during bacterial peritonitis. Data presented in the current study indicate that at the time when adynamic ileus was established, the superior mesenteric artery flow was the same as control values, whereas during the inflammatory stage the superior mesenteric artery flow had increased significantly. Gump, Price and Kinney[9] similarly demonstrated that a significant increase in splanchnic blood flow was noted in man when fever and infection were associated with hypermetabolism. In the present series of experiments, intraluminal pressure never exceeded 30 mm Hg. Consequently blood flow probably was not affected significantly by the intraluminal pressure. A study of Boley and his associates[2] indicated that no change in intestinal blood flow occurs below an intraluminal pressure of 30 mm Hg.

Clowes and his associates[5] studied 25 patients with peritonitis. At the beginning, while peritonitis was developing, a low cardiac output was frequently present. As the illness progressed, a greater than normal cardiac output was required to satisfy the metabolic needs of

TABLE 3. *Mechanical Activity of the Ileum*

Hours After Appendiceal Ligation	No. of Contractions (No./min)	Maximum Contractile Pressure (mm Hg)
Control	10.2 ± .34	8.1 ± 1.68
3	9.0 ± .63	7.8 ± 1.41
6	1.1 ± 1.05*	.3 ± .35*
9	.0 ± .00*	.0 ± .00*
12	.0 ± .00*	.0 ± .00*

* Significant with $p < .005$ as compared to control value
Values represent mean ± standard error of eight animals

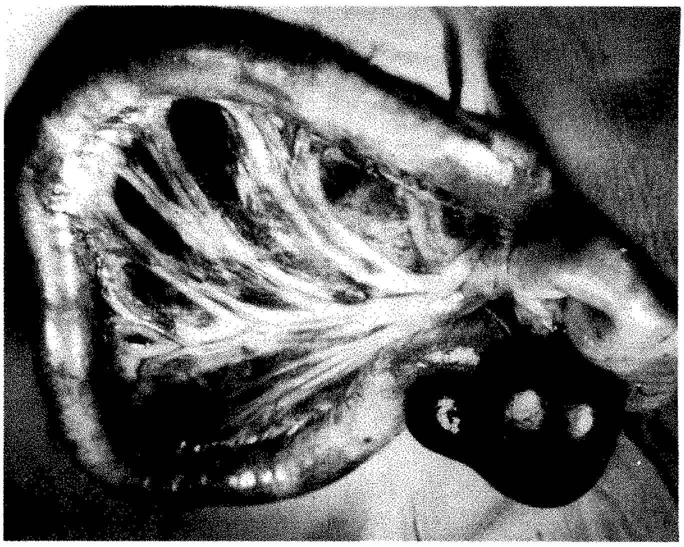

FIG. 2. A macroscopic photograph of the ileum and the appendix 12 hours after appendix ligation (Dog AL-18). Note dilatation of the ileum, gas and fluid accumulation and the massive necrosis of the appendix.

the body. If peritonitis and inflammation were prolonged, failure to maintain a high cardiac output ultimately occurred and resulted in progressive metabolic derangements. It is well documented that survival in the presence of sepsis and inflammation demands a considerable, sustained increase in the circulation.[1] It appears that the same is true in extensive peritonitis. When this requirement is not satisfied for any cause, as long as the inflammatory process is present, progressive loss of cellular energy production and organ function will follow.[5]

Part of the inflammatory reaction is a local increase of capillary permeability with the escape of water and other elements from the blood system. Fluid is translocated into the intestinal wall, the lumen of the gut and the peritoneal cavity. Endotoxin seems to be partly responsible for these mechanisms. MacLean and his associates[16] demonstrated that after endotoxin administration, the small intestine continues to gain weight as a result of accumulation of intestinal fluid. As edema and peritoneal fluid are developing, hypovolemia and electrolyte derangements may frequently result in cardiac indices falling well below their normal resting values. Splanchnic pooling has also been held responsible for reduced venous return with a resultant decrease in cardiac output.[27]

The work of Rosoff and his associates[23] indicated that the total arterial vasoconstriction was not a predominant feature in the patients with severe bacterial peritonitis, especially in those with associated hypotension. However, such low total resistance does not rule out the existence of areas of vasoconstriction marked by coexisting areas of vasodilatation or arteriovenous shunting

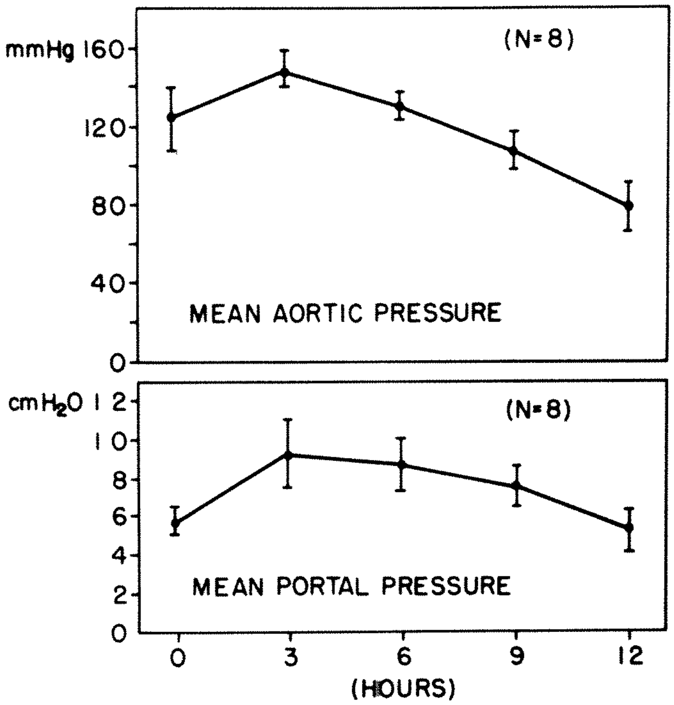

FIG. 3. Changes of mean aortic pressure and mean portal pressure before and after ligation of the appendix. Values represent mean ± standard error.

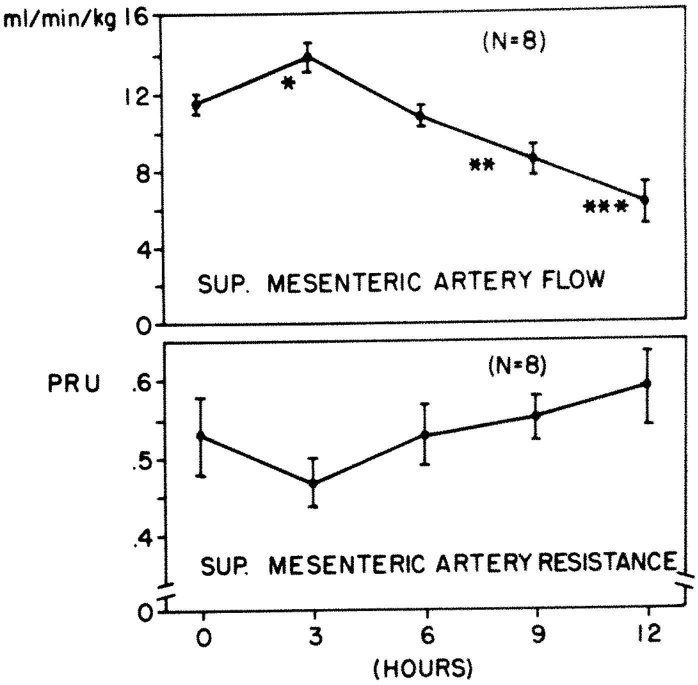

FIG. 4. Changes of superior mesenteric artery flow and superior mesenteric artery vascular resistance before and after ligation of the appendix. Values represent mean ± standard error.
* Significant with $P < .05$ compared to control value.
** Significant with $P < .01$ compared to control value.
*** Significant with $P < .005$ compared to control value.

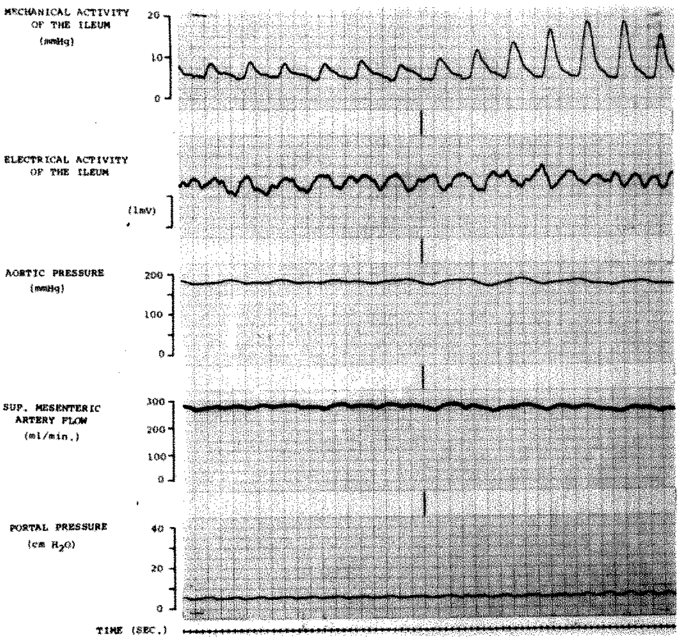

FIG. 5. Ileal motility and splanchnic hemodynamics before the appendix ligation (Dog AL-18).

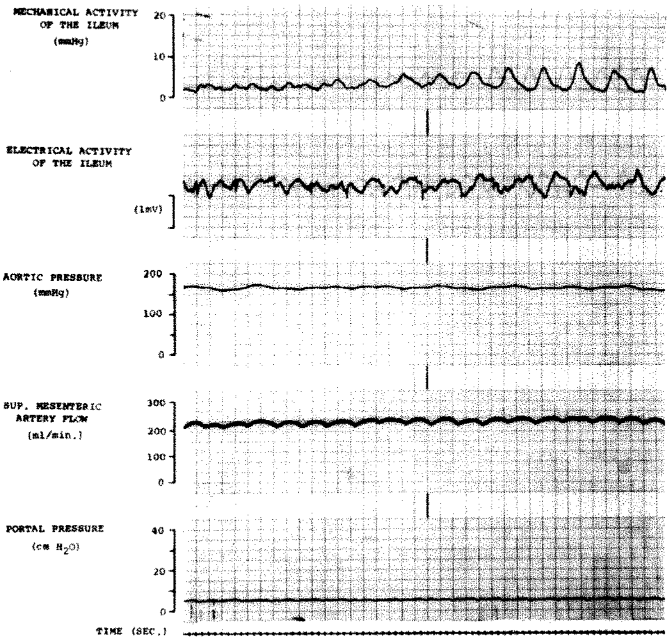

FIG. 6. Ileal motility and splanchnic hemodynamics 3 hours after appendix ligation (Dog AL-18).

or both. The studies of Rosoff and his associates[23] support the possibility that an important part of arteriovenous shunting of bacterial peritonitis may be associated with a hyperemic inflammatory response of the peritoneum. Johnson[12] concluded that resistance changes in the intestine might not be dependent on nervous mechanisms and suggested that the elevation of venous pressure induced a myogenic response in the resistance vessels.

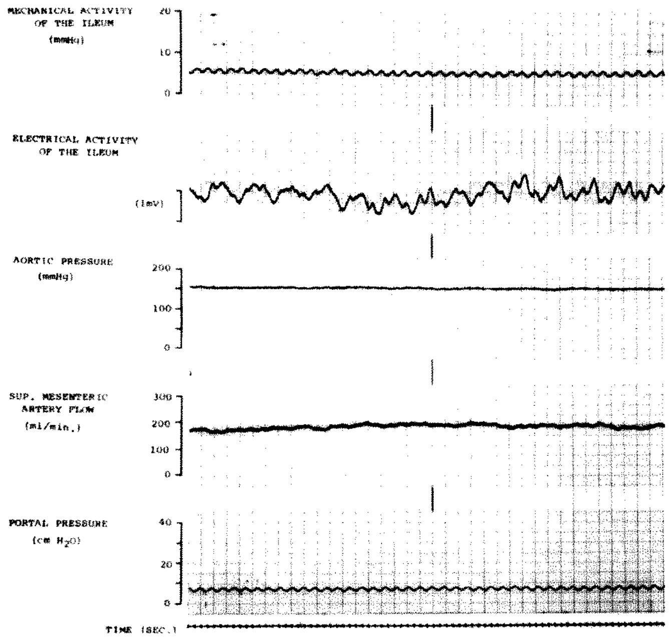

FIG. 7. Ileal motility and splanchnic hemodynamics 6 hours after appendix ligation (Dog AL-18).

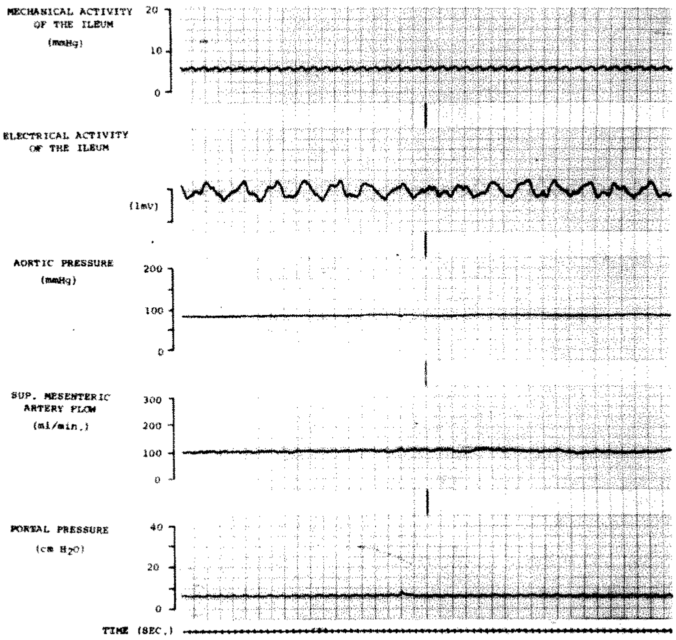

FIG. 8. Ileal motility and splanchnic hemodynamics 9 hours after appendix ligation (Dog AL-18).

In the present experiment a decrease in splanchnic vascular resistance was demonstrated. This resistance, however, returned to the control value during the stage of adynamic ileus. Moreover, a progressive increase in vascular resistance was demonstrated during the time when ileus occurred. Nevertheless, as Selkurt and Brecher[24] demonstrated in the course of hemorrhagic shock, this upward trend may not be maintained, but a

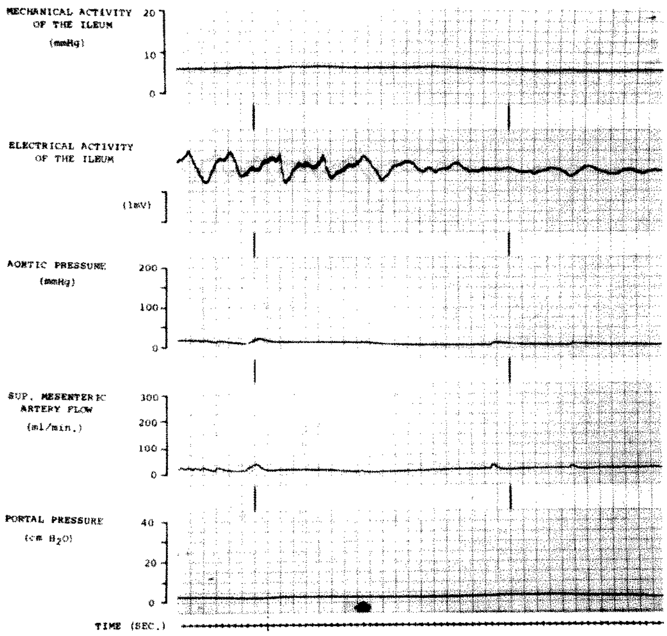

FIG. 9. Ileal motility and splanchnic hemodynamics 12 hours after appendix ligation (Dog AL-18). Arrow indicates cardiac arrest.

fall in vascular resistance eventually occurred in the majority of animals as they entered the terminal stage of vascular collapse. In three animals of this series the superior mesenteric artery resistance was 25% below the control value at the end of twelve hours. When cardiac output proves incapable of maintaining adequate perfusion of all tissues, arterial blood pressure is maintained by an increase in the total peripheral vascular resistance. This is brought about by a marked hyperactivity of the sympatho-adrenal system mediated through an increased activity of the vasomotor center. Biochemical evidence of this hyperactive state is revealed by the finding of elevated blood catecholamine levels resulting principally from epinephrine secreted by the adrenal medulla.[11] Irving[11] observed that animals premedicated with alpha-adrenergic blockers did not develop paralytic ileus in response to hemorrhage or adrenalin infusion as did the non-medicated animals.

It is generally agreed that stimulation of the splanchnic nerves causes vasoconstriction in the intestine. Green and Kepchar[8] stated that splanchnic nerve stimulation and administration of adrenergic substances produce vasoconstriction in the intestine, presumably by excitation of alpha-adrenergic constrictor receptors. The usual secondary dilatation observed after epinephrine injection and especially the primary dilatation seen when epinephrine is administered following Ilidar or ergotamine blockage indicated the presence of beta-adrenergic dilator receptors as well.

On the other hand, Neely and Catchpole[19] investigated the autonomic control of gastrointestinal motility in the cat. The stomach appears to have a high level of extrinsic, but a low level of intrinsic, cholinergic innervation. Both alpha- and beta-adrenergic receptors are present. The small intestine on the other hand, has a low level of extrinsic and high level of intrinsic, cholinergic control; sympathetic inhibition is mediated largely through the alpha-receptors. The colon has a low degree of cholinergic control and the sympathetic inhibition is mediated mainly through beta-receptors. It is postulated therefore, that in the course of peritonitis, the associated ileus might result from a combination of direct receptor stimulation from circulating catecholamines and a sympathetic nerve mediated action as well. Potassium depletion seems to be one of the contributory conditions.[15]

Circulatory and intestinal failure observed in the late stage of related experiments appears to result from the presence of circulating toxins,[6,10] vasoactive peptides,[4,13,25] pigments,[7] or other products of necrotic tissue. Whether the effects of these substances are mediated by a neural or direct muscular action on the vessels and the intestine is not illuminated by this investigation.

Summary

A hemodynamic study was performed in the course of acute peritonitis due to appendiceal ligation. Adynamic ileus developed approximately 6 hours after the procedure.

The mechanical activity of the ileum was greatly reduced within the first six hours and was associated with a similar reduction in the number of spike potentials which could be observed. Slow wave electrical activity, however, was sustained and was relatively unchanged in rate and amplitude until the time of death.

Intestinal motility and splanchnic hemodynamics appeared to undergo four stages of deterioration. An initial response to injury, a stage of inflammation, a stage of adynamic ileus and the stage of peripheral vascular collapse could be distinguished. The superior mesenteric artery flow increased and resistance decreased in the stage of inflammation. Subsequently, superior mesenteric artery flow and resistance returned to approximately control values during the stage of ileus. In the early stage of vascular collapse, flow began to decrease and the resistance was increased. It is proposed that these hemodynamic changes are related more to the humoral factors than to simple splanchnic nerve stimulation.

References

1. Albrecht, M. and Clowes, G. H. A., Jr.: The Increase of Circulatory Requirements in the Presence of Inflammation. Surgery, **56**:158, 1964.
2. Boley, S. J., Agrawal, G. P., Warren, A. R., Veith, F. J., Levowitz, B. S., Treiber, W., Dougherty, J., Schwartz, S. S. and Gliedman, M. L.: Pathophysiologic Effects of Bowel Distension on Intestinal Blood Flow. Am. J. Surg., **117**:228, 1969.
3. Catchpole, B. N.: Ileus: Use of Sympathetic Blocking Agents in its Treatment. Surgery, **66**:811, 1969.
4. Chou, C. C. and Dabney, J. M.: Interrelation of Ileal Wall Compliance and Vascular Resistance. Am. J. Diget. Dis. (new series), **12**:1198, 1967.
5. Clowes, G. H. A., Jr., Vucinic, M. and Weidner, M. G.: Circulatory and Metabolic Alternations Associated with Survival or Death in Peritonitis: Clinical Analysis of 25 Cases. Ann. Surg., **163**:866, 1966.
6. Daniele, R., Singh, H., Appert, H. E., Pairent, F. W. and Howard, J. M.: Lymphatic Absorption of Intraperitoneal Endotoxin in the Dog. Surgery, **67**:484, 1970.
7. Filler, R. M., Sleeman, H. K., Hendry, W. S. and Pulaski, E. J.: Lethal Factors in Experimental Peritonitis. Surgery, **60**:671, 1966.
8. Green, H. and Kepchar, J.: Control of Peripheral Resistance in Major Systemic Vascular Beds. Physiol. Revs., **39**:617, 1959.
9. Gump, F. E., Price, J. B. and Kinney, J. M.: Whole Body and Splanchnic Blood Flow and Oxygen Consumption Measurements in Patients with Intraperitoneal Infection. Ann. Surg., **171**:321, 1970.
10. Hicks, C., Braumann, F. G. and Enquist, I. F.: Changes in

Intestinal Flora in Dogs with Nonstrangulating Intestinal Obstruction. Surgery, 66:580, 1969.

11. Irving, M. H.: The Sympatho-adrenal Factor in Hemorrhagic Shock. Ann. R. Coll. Surg., Engl., 42:367, 1968.
12. Johnson, P. C.: Myogenic Nature of Increase in Intestinal Vascular Resistance with Venous Pressure Elevation. Circ. Res., 7:992, 1959.
13. Lewis, G. P.: The Role of Plasma Kinins as Mediator of Functional Vasodilation. Gastroenterology, 52:406, 1967.
14. Lintermans, J. P., Appel, A. J., Bloom, R. S., Mullins, G. L. and Guntheroth, W. G.: Mesenteric Blood Flow and Vascular Volume in Hemorrhagic Shock. Am. J. Physiol., 212: 482, 1967.
15. Lowman, R. M.: The Potassium Depletion States and Postoperative Ileus: The Role of the Potassium Ion. Radiology, 98:691, 1971.
16. MacLean, L. D., Weil, M. H., Spink, W. W. and Visscher, M. B.: Canine Intestinal and Liver Weight Changes Induced by E. coli Endotoxin. Proc. Soc. Exp. Biol. Med., 92:602, 1956.
17. Markowitz, J. and Campbell, W. R.: The Relief of Experimental Ileus by Splanchnic Anesthesia. Am. J. Physiol., 81:101, 1927.
18. Murphy, J. J., Ravdin, R. G. and Zintel, H. A.: The Use of Streptomycin in Experimental Peritonitis. Surgery, 20:445, 1946.
19. Neely, J. and Catchpole, B. N.: An Analysis of the Autonomic Control of Gastrointestinal Motility in the Cat. Gut, 8:230, 1967.
20. Nishijima, H.: Electromyographical Studies on the Intestinal Tract. Tokushima J. Exptl. Med., 10:38, 1963.
21. Ochsner, A., Gage, I. M. and Cutting, R. A.: Comparative Value of Splanchnic and Spinal Anesthesia in the Treatment of Experimental Ileus. Arch. Surg., 20:802, 1930.
22. Oppenheimer, M. J. and Mann, F. C.: Intestinal Capillary Circulation During Distension. Surgery, 13:548, 1943.
23. Rosoff, L., Weil, M., Bradley, E. C. and Berne, C. J.: Hemodynamic and Metabolic Changes Associated with Bacterial Peritonitis. Am. J. Surg., 114:180, 1967.
24. Selkurt, E. E. and Brecher, G. A.: Splanchnic Hemodynamics and Oxygen Utilization during Hemorrhagic Shock in the Dog. Circ. Res., 4:693, 1956.
25. Shah, J. P., Shah, U. S., Appert, H. E. and Howard, J. M.: Studies on the Release of Bradykinin by the Splanchnic Circulation during Endotoxic Shock. J. Trauma, 10:255, 1970.
26. Sorbie, C.: Peristalsis and Sympathetic Activity. Lancet, 1:821, 1968.
27. Weil, M. H., MacLean, L. D., Visscher, M. B. and Spink, W. W.: Studies on the Circulatory Changes in the Dog Produced by Endotoxin from Gram-Negative Microorganisms. J. Clin. Invest., 35:1191, 1956.

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APPLY ENZYME
Apply a layer of TRAVASE Ointment. Assure intimate contact with necrotic tissue and complete wound coverage.

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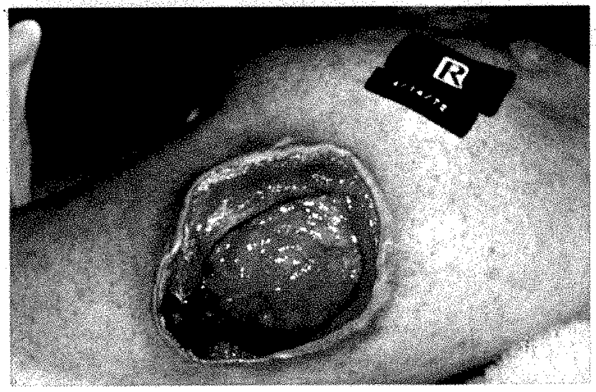
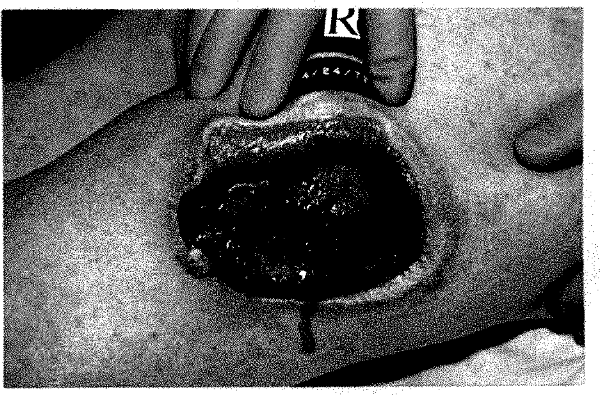


Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



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burns

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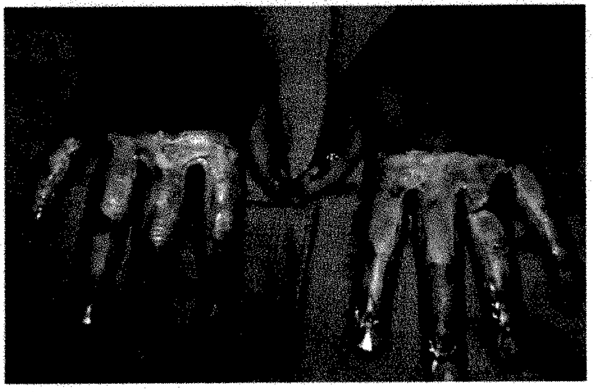
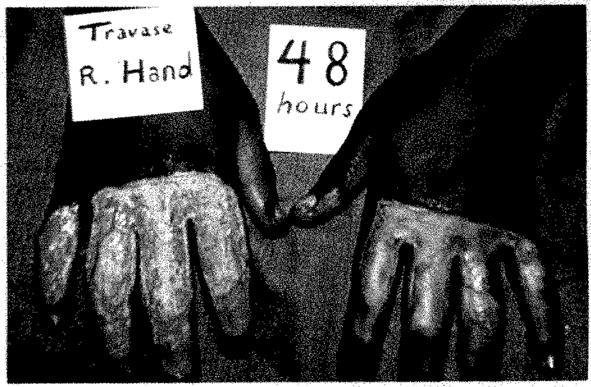


Before treatment . . .



48 hours following treatment with TRAVASE Ointment on right hand; left hand is control.

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Ulcers secondary to peripheral
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Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

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Wounds containing exposed major nerves or nervous tissue,
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Warning: Do not permit TRAVASE Ointment to come into contact with the eyes. If contact is made, immediately rinse with copious amounts of water, preferably sterile.

Precautions: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents (see package insert). Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

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1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g. sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

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Anastomotic Ulceration

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ANASTOMOTIC ULCER PROVIDES THE CLINICIAN with an even greater therapeutic challenge than primary peptic ulcer. Not only has the original operation failed to cure the patient's ulcerative diathesis, but subsequent management has been complicated by alterations in the physiology and anatomy of the upper gastrointestinal tract. It is therefore hardly surprising that there is a high mortality and morbidity associated with this complication. Although anastomotic ulcers have been studied since the first quoted case of Braun[5] in 1891 there is still insufficient information to guide the clinician in his management of this complication.

In the period 1957–1968, 331 patients with anastomotic ulcer were admitted to the Vancouver General or Shaughnessy Veteran's Hospital. This includes patients treated medically as well as surgically and enables a comparison to be made of the results of treatment after conservative as well as surgical therapy. The primary operation for peptic ulcer was carried out in the two hospitals in 44%. In all but 11% of the total series, the original case records were available. This information was supplemented over the years by more detailed case studies at the Gastrointestinal Clinic of the University of British Columbia. We do not know the size of the original "pool" of primary peptic ulcer patients.

Etiological Factors

We found certain factors important in the development of recurrent ulcers. Patients with a recurrent ulcer often developed further recurrence following therapy. Most of the patients developed recurrent ulcers following operation for duodenal ulcer, but some developed recurrence following operation for other varieties of peptic ulcer. As a group, the patients with recurrent ulcer were drug abusers. Patients with anastomotic ulcer tended to belong to blood group "O". There was a relatively high incidence of women with recurrent ulcer compared to the incidence found in primary peptic ulcer. In post-gastrectomy anastomotic ulcer, only a few recurrences were attributable to retained antra. Post-Billroth I recurrent ulcer patients had a lesser gastric resection than post-Billroth II anastomotic ulcer patients.

Distribution

Fifty-one of the 331 patients developed recurrent ulcers after surgical treatment and six of these developed a third recurrent ulcer. One patient went on to have a fourth and fifth anastomotic ulcer after surgical treatment. There were therefore 390 anastomotic ulcers in 331 patients (Table 1).

The follow-up varied from one to 14 years, half being followed six years or more. Only 20% of 331 patients were regular clinic attenders, and the other patients were followed-up by questionnaire or interview in 1971. Of the 331 patients, 22% were untraced but many of these had been previously followed-up for several years, 16% of the 74 untraced patients having been followed for six years or more.

Site of the Primary Ulcer

This reflects the usual finding that the primary operation was for duodenal ulcer in the majority of cases, 88% in our study (Table 2).

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TABLE 1. *Distribution of Anastomotic Ulcers by Primary Operation*

Primary Operation	No. with one Anastomotic Ulcer	No. with Two Anastomotic Ulcers	No. with Three Anastomotic Ulcers	No. with Five Anastomotic Ulcers
Billroth I	48 (90.6)	5 (9.4)		
Billroth II	124 (88.6)	15 (10.7)	1 (0.7)	
Vagotomy and Pyloroplasty	30 (85.7)	4 (11.4)	1 (2.9)	
Vagotomy and Gastroenterostomy	6 (66.7)	3 (33.3)		
Vagotomy and Partial Gastrectomy	14 (93.3)	1 (6.7)		
Gastroenterostomy	58 (73.4)	17 (21.5)	3 (3.8)	1 (1.3)
Total	280 (84.6)	45 (13.6)	5 (1.5)	1 (0.3)

Figures in parentheses are percentages

Results of Primary Operation

The immediate post-operative results of surgery for primary peptic ulcer disease were satisfactory in all but 19% of operations (Table 3). The early results of gastric surgery therefore gave no prediction of the eventual outcome in terms of ulcer recurrence. The excellent immediate results of simple gastroenterostomy (79%) are of particular interest.

Drug Habits

The incidence of tobacco smoking, and ingestion of aspirin products, alcohol and coffee and tea were studied in the anastomotic ulcer patients. Of the 331 patients 28% smoked more than one package of cigarettes per day. More than five cups of tea or coffee per day were drunk by 11% of the patients. Aspirin products were ingested every day for weeks at a time by 15% of patients, 11% took aspirin products more than once a week, and the rest avoided aspirin products or took them rarely. More than eight fluid ounces of spirits or the equivalent amount of alcohol per day was drunk by 19%, 14% were regular drinkers and the rest avoided alcohol or drank it rarely

These results are startlingly different from a similar survey by Small[21] in 1964, who found no aspirin ingestion in his series of 83 patients with jejunal ulcer, but a higher proportion of tobacco smoking than in our series.

Blood Group

The blood group was recorded in 324 of the 331 patients with anastomotic ulcer: 55% belonged to Blood Group O. In a study of blood groups of more than 15,000 donors at randomly selected clinics in the greater Vancouver area, the frequency of Blood Group O was found to be 44%. The increased frequency of Blood Group O in anastomotic ulcer has been noted in the past but the reason for this finding is still unclear.

TABLE 2. *Site of Ulcers at Primary Operations*

Primary Operation	One Duodenal	Two Duodenal	Duodenal & Gastric	Duodenal & Pyloric	Pyloric	Pyloric & Gastric	Gastric	Not Known
Billroth I	32 (60.4)		2 (3.8)		11 (20.7)		7 (13.2)	1 (1.9)
Billroth II	117 (83.6)	3 (2.1)	7 (5.0)	2 (1.4)	3 (2.1)		7 (5.0)	1 (0.7)
Vagotomy and Pyloroplasty	28 (80.0)	1 (2.9)	1 (2.9)		3 (8.6)	2		
Vagotomy and Gastroenterostomy	8 (88.9)				1 (11.1)			
Vagotomy and Partial Gastrectomy	13 (86.7)		1 (6.7)				1 (6.7)	
Gastroenterostomy	75 (94.9)				3 (3.8)			1 (1.3)
Total	273 (82.5)	4 (1.2)	11 (3.3)	2 (0.6)	21 (6.3)	2 (0.6)	15 (4.5)	3 (0.9)

Figures in parentheses are percentages

TABLE 3. *Visick Grading after Primary Operation. (In this, and the Tables Following, Grade I, II and IIIS are Considered Satisfactory Results. Grades IIIU and IV are Unsatisfactory)*

Primary Operation	Not Known	I	II	IIIS	IIIU	IV
Billroth I	1 (1.9)	20 (37.7)	15 (28.3)	3 (5.7)	1 (1.9)	13 (24.5)
Billroth II		40 (28.6)	63 (45.0)	9 (6.4)	7 (5.0)	21 (15.0)
Vagotomy and Gastroenterostomy		5 (55.6)	3 (33.3)	1 (11.1)		
Vagotomy and Pyloroplasty	1 (2.9)	16 (45.7)	10 (28.6)	2 (5.7)	2 (5.7)	4 (11.4)
Vagotomy and Partial Gastrectomy		1 (6.7)	3 (20.0)	2 (13.3)	6 (40.0)	3 (20.0)
Gastroenterostomy	1 (1.3)	62 (78.5)	7 (8.9)	2 (2.5)	1 (1.3)	6 (7.6)
Total	3 (0.9)	144 (43.5)	101 (30.5)	19 (5.7)	17 (5.1)	47 (14.2)

Figures in parentheses are percentages

Sex Incidence

In this study 21% of the patients were females. We have no means of ascertaining the size of the population from which these patients were drawn but there does seem to be a higher percentage of females than one could expect from the relative frequency of surgical intervention for primary peptic ulcer disease which is 15% for women in the Vancouver General Hospital. A possible explanation for this is that surgeons tend to be more conservative in the surgery of women both in terms of gastric resection and a tendency to carry out a Billroth I anastomosis rather than a Billroth II type.

Retained Antrum in the Duodenal Stump Following Partial Gastrectomy

The pathology reports from the original operation were available for most of the gastrectomy specimens. Many of the reports did not mention the presence or absence of duodenal mucosa in the excised specimen but it was possible to exclude antral tissue in the duodenum in 67% of Billroth II gastrectomies. Of the remaining 46 post Billroth II anastomotic ulcer patients, re-operation was carried out in 34 and the duodenal stump was examined in 31 of these, 16 of whom had a biopsy or excision done: six of these patients were found to have retained antra. Twelve patients were treated medically and we have no histologic evidence in 11 of these, but one autopsy showed no retained antrum in the duodenal stump. In the remaining patients we have no clinical evidence of retained antra but this has not been checked by histology or at operation. In summary, of the total 140 Billroth II gastrectomies retained antral tissue was present in the duodenal stump in six (4%) and there is good evidence that there was no retained antrum in the remaining 96%. This is a much lower incidence of retained antrum than that found by Boles[4] and his colleagues in 1960 who reported retained antra in 14 of 36 patients. This indicates improvement of surgical technique in this respect in the last 20 years due to awareness of this problem.

Of the six patients with retained antra, three had retained antra detected at their first anastomotic operation and three had the retained antra detected only after developing a second anastomotic ulcer. Table 4 summarizes the treatment of the patients in this group. One of the six patients has had an ulcer recurrence demonstrated at operation since removal of retained antrum.

Adequacy of Partial Gastrectomy

The adequacy of gastrectomy in terms of percentage of stomach resected must always be a compromise between prevention of anastomotic ulcer and the increased incidence of malnutrition, malabsorption and tuberculosis which follows a high gastrectomy. On the basis of the surgeon's estimate of percentage of stomach resected, 76% had a resection of 66% or more and only 3% had a resection of less than 50% of the stomach (Table 5). It may be important, however, to note that resection for a Billroth I was significantly less than resection for a Billroth II. This was presumably due to the fear of the surgeon that insufficient gastric remnant would be available for anastomosis to the duodenum without tension. This may be one of the reasons why Billroth I gastrectomy is more liable to result in recurrent ulceration.

Clinical Characteristics

We must stress that the clinical characteristics are still the best single method of diagnosing anastomotic ulcer. We found that haemorrhage was a prominent symptom of most of the patients with anastomotic ulcer. The site of the ulcer was influenced by the type of antecedent operation. The age of development of anastomotic ulcer varied with the type of antecedent

TABLE 4. *Retained Antrum in the Duodenal Stump. Summary of the Clinical Course in the Six Patients with Retained Antra Following Billroth II Gastrectomy.*

Sex	Date of Birth	Antecedent Operations	Findings	Follow-up
M	1897	1964, 60% BIIA for D.U. of 13 years duration. Oct. 1965, 75% BIIA for massive haemorrhage, 3 ulcers present, (2 stomal and 1 gastric).	Nov. 1965, retained antrum and 60 ml. blood in stomach. No bleeding point found. Antrum excised and anastomosis revised as Roux-en-Y.	1966, haemorrhage. Jejunal ulcer at operation and vagotomy with 85% BIIA. 1971, Visick I on F.U.
M	1905	1962, 70% BIIR and vagotomy for D.U. of 1 year duration. 1963, prandial pain. 1963, efferent jejunal ulcer, 90% BII and Roux-en-Y. 1964, pain and vomiting.	1966, retained antrum and efferent jejunal ulcer. Antrum excised and 95% BIIR.	1971, Visick I on F.U.
M	1926	1957, 66% BIIR and Roux-en-Y for D.U. of 7 years duration. 1958, pain and haemorrhage.	1961, stomal ulcer and retained antrum. Antrum excised and vagotomy.	1971, Visick II on F.U.
F	1924	1956, 66% BIIR for D.U. of 17 years duration. 1958, prandial pain.	1961, jejunal ulcer and retained antrum. Antrum excised and vagotomy.	1962, repeated episodes of bleeding eoesophageal varices. On portogram pressure in portal vein was 340 mm Hg. Lost to follow-up.
F	1942	1962, 66% BIIA for D.U. of 12 years duration. 1965, pain and vomiting.	1968, distended afferent loop with jejunal ulcer on afferent side and retained antrum. Antrum excised and 75% BIIA.	1970, prandial pain and vomiting. 1971, Barium meal showed stomal ulcer crater.
M	1932	1968, V. and P. for D.U. of 1 year duration. 1968, prandial pain. 1969, 50% BIIA for perforated D.U. 1969, pain and haemorrhage.	1970, retained antrum—no ulcer found. Antrum excised and 66% BI with vagotomy	1971, Visick II on F.U.

operation as did the interval between antecedent operation and definitive treatment of recurrent ulcer.

Symptoms

The pattern of symptoms of anastomotic ulcer was similar to that of the primary operation. Post-prandial pain occurred in 74% of the patients, 24% had no pain and there was insufficient information concerning symptoms in 2%.

Twelve patients had diarrhoea and weight loss and seven of these were found to have gastro-jejuno-colic fistula. These symptoms of diarrhoea and weight loss were therefore considered to be highly suggestive of the diagnosis of gastro-jejuno-colic fistula. There were only 2% gastro-jejuno-colic fistulae in this study, indicative of the decreasing frequency of this dangerous complication in recent studies.

It is noteworthy that 56% of the 390 anastomotic ulcer patients had one or more episodes of haemorrhage. There was a perforation of an anastomotic ulcer in 5% and this is a standard observation. The incidence of stenosis was 9%.

Site of Anastomotic Ulcers

Table 6 shows the site of the 390 anastomotic ulcers. Clearly the site at which an anastomotic ulcer develops depends partly on the primary operation. The ulcers seen at operation were chronic in 91%, 7% were acute, and 2% were suture ulcers.

TABLE 5. *Percentage of Stomach Resected (Estimated) at the Primary Operation*

Antecedent Operation	Not Known	1/3 P. G.	1/2 P. G.	2/3 P. G.	3/4 P. G.	S. T.
Billroth I	1 (1.9)	1 (1.9)	28 (52.8)	18 (34.0)	5 (9.4)	
Billroth II		5 (3.6)	9 (6.4)	116 (82.9)	10 (7.1)	
Vagotomy and Partial Gastrectomy			6 (40.0)	7 (46.7)	1 (6.7)	1 (6.7)
Total	1 (0.5)	6 (3.0)	43 (20.5)	141 (67.5)	16 (8.0)	1 (0.5)

P. G.—Partial gastrectomy
S. T.—Subtotal gastrectomy
Figures in parentheses are percentages

TABLE 6. *Site of Anastomotic Ulcers*

Antecedent Operation (s)	Gastric	Stomal	Jejunal Efferent	Jejunal Afferent	Duodenal	Jejunal & Gastric	Jejunal & Duodenal	Not Known
Billroth I	11 (19.6)	20 (35.7)	0 (0)	0 (0)	15 (26.8)	0 (0)	0 (0)	10 (17.9)
Billroth II	14 (8.2)	36 (21.1)	74 (43.3)	1 (0.6)	0 (0)	3 (1.7)	0 (0)	43 (25.1)
Vagotomy and Pyloroplasty	7 (19.4)	0 (0)	0 (0)	0 (0)	18 (50.0)	0 (0)	0 (0)	11 (30.6)
Vagotomy and Gastroenterostomy	1 (9.1)	3 (27.3)	4 (36.4)	0 (0)	0 (0)	0 (0)	0 (0)	3 (27.3)
Vagotomy and Partial gastrectomy	6 (16.7)	8 (22.2)	10 (27.8)	0 (0)	2 (5.6)	0 (0)	0 (0)	10 (27.8)
Gastroenterstomy	17 (31.2)	10 (12.5)	32 (40.0)	0 (0)	6 (7.5)	0 (0)	3 (3.8)	12 (15.0)
Total	56 (14.4)	77 (19.7)	120 (31.1)	1 (0.3)	41 (10.5)	3 (0.7)	3 (0.7)	89 (22.8)

Figures in parentheses are percentages

Gastric ulcer was significantly commoner after gastroenterostomy alone than after Billroth II gastrectomy when numbers observed were compared to numbers expected by chance alone. A possible reason for this is that the area of the stomach at risk is larger in gastroenterostomy alone than after Billroth II gastrectomy. However, when the site of recurrence after Billroth I was compared to that after vagotomy with pyroroplasty there was no difference in the rate of gastric ulceration. Golligher[10] has noted increased frequency of development of gastric ulcer following the Billroth I procedure and considers this operation may predispose to the development of gastric ulceration. However, in our series, the vagotomy with pyloroplasty group has been followed for a much shorter time than the Billroth I group and the incidence of gastric ulcer after vagotomy and pyloroplasty procedures may rise as the results become available for long term follow-up. Another factor might be that the mean age following gastroenterostomy (61 ± 14) is higher than after the Billroth II operation (50 ± 11) and the mean age of the patients with a Billroth I procedure (52 ± 11) is not significantly higher than that of the vagotomy with pyloroplasty group (48 ± 13). It is known that gastric ulcers are more freqeunt in the elderly and this would explain our findings.

Age at Operation for First Anastomotic Ulcer

This was calculated only for those undergoing surgical treatment. The age of the patients with anastomotic ulceration following gastroenterostomy alone (61 ± 14) is greater on average than the patients with anastomotic ulceration following other procedures (54 ± 11). This reflects the changing fashion in surgical operations over the last 20 years and the decline in frequency of gastroenterostomy as a routine treatment of duodenal ulcer.

Interval Prior to Treatment of Anastomotic Ulcer

The interval between the primary operation of peptic ulcer and year of treatment of anastomotic ulcer varied markedly depending on the type of antecedent operation (Table 7). Although there is general agreement that after gastroenterostomy an anastomotic ulcer can occur many years after the initial treatment, it has been held that after gastrectomy an anastomotic ulcer tends to recur much earlier. Our study shows a long interval after gastrectomy does not convey immunity from subsequent anastomotic ulcer. We would suggest that this is due to the late results of gastrectomy now becoming available and predict that the present short intervals prior to the development of anastomotic ulcer following the vagotomy procedures will prove artifactual, and as long term studies become available more and more patients will be found to develop anastomotic ulcer at long intervals after these procedures.

Diagnostic Procedures

We define anastomotic ulcer as a benign peptic ulcer which develops after definitive gastric surgery. Two

TABLE 7. *Interval between Primary Operation and Operation for First Anastomotic Ulcer*

Antecedent Operation	No.	Interval—Mean & S.D. (In Years)	Range in years
Billroth I	53	5.40 ± 5.60	0–33
Billroth II	140	3.39 ± 3.04	0–24
Vagotomy and Pyloroplasty	35	1.48 ± 0.77	0–4
Vagotomy and Gastroenterostomy	9	3.56 ± 2.30	0–7
Vagotomy and Partial gastrectomy	15	2.78 ± 2.91	0–10
Gastroenterostomy	79	17.27 ± 11.18	0–40

hundred and forty-four of the 390 anastomotic ulcers in the series were visualized at operation or autopsy. An ulcer crater was detected on barium meal examination in a further 64 instances. An ulcer was seen on gastroscopy in 15, and in 67 remaining cases, the diagnosis was made on clinical grounds alone. Acid secretory tests, both maximal acid secretion and Hollander tests, were of value.

Barium Meal X-Ray

The diagnostic value of this test was low. In 331 barium meal examinations, 52% showed an ulcer crater. We consider the results indefinite in a further 19% since distortion or spasm were the only abnormalities demonstrated. No abnormality was demonstrated in the remaining 29%. These results agree with the findings of Walters and Chance[27] in 1955.

Gastroscopy

Gastroscopy proved disappointing in determining the presence of an anastomotic ulcer. Of 72 gastroscopies, an ulcer crater was seen in 37%. In a further 25%, spasm or irritability of the anastomosis or inflammation around the anastomosis was noted which would have given rise to suspicion of an ulcer beyond the range of the gastroscope. However, it must be noted that the gastroscopies performed in this series were carried out prior to the use of fiberoptic endoscopy in our department. It is probable therefore that with the use of the more modern instruments now available, the incidence of positive diagnosis will improve.

Maximal Acid Secretory Studies

The peak acid output in response to Histalog* or more recently Pentagastrin was measured in 142 of the anastomotic ulcers. We found that the peak acid output measurement in patients after partial gastrectomy with or without vagotomy, was of some value in discriminating between patients with anastomotic ulcer and controls. More than 95% of the control values (110 controls) were below 12 mEq. acid output in the peak post-stimulation hours and more than 40% of the anastomotic ulcers had acid secretory results above this value.

Hollander Test

This proved most valuable in the post-vagotomy with pyloroplasty group. Insulin testing was carried out in 22 of these patients, and the test was positive on Hollander's criteria in 21 of these, indicating an incomplete vagotomy. The solitary negative test occurred in a patient with a gastric anastomotic ulcer, but was not repeated prior to reoperation.

Serum Gastrin

Serum gastrin estimations should now be available for every patient with anastomotic ulcer, using either radio-immune assay[14] or, if not available, bioassay.[6,25] This would serve the two-fold purpose of excluding the Zollinger-Ellison syndrome, and excluding the possibility of retained antra in the duodenal stump of post gastrectomy patients. Although we have been carrying out radio-immune assay and bioassay of gastrin for the last year, we do not yet have the serum gastrin levels for the patients in this study.

Therapy Employed

The effectiveness of treatment of anastomotic ulcer is usually judged by the mortality rate from the operation or treatment and the recurrent ulcer rate. In this study we have included deaths due to ulcer and deaths due to operation in each group. For medical treatment the mortality rate is deaths due to ulcer, and deaths from other causes are not included. Following surgical treatment, the deaths represent the operative mortality, and after the first month deaths from incidental causes are not included. The period of follow-up is critical to any assessment of the results. When our results were grouped into follow-up periods of five years or less and follow-up periods of six years or more there was a significantly higher recurrence rate in the group with longer follow-up. Of the 194 patients followed for five years or less, 18 had one recurrent ulcer (9%). Of the 137 patients followed six years or more, 27 had one recurrent ulcer and six had two or more recurrent ulcers (24%). In the further discussion of the results of treatment therefore, our results have been broken down into follow-up periods of greater than one year to permit comparison with the results of other studies, and six years or more to give the recurrence rate on long term follow-up.

Post-Gastrectomy Anastomotic Ulcer

These ulcers should be treated by transabdominal vagotomy. Seventy-one patients in our study were treated in this way with no operative deaths, seven proven recurrent ulcers and seven suspected recurrent ulcers (Tables 8–10). A further ten patients required some modification of the anastomosis in addition to vagotomy and of these patients there were no operative deaths. One had a recurrent ulcer and one had a suspected recurrent ulcer. A more proximal or higher gastrectomy was carried out in 78 patients, 40 of whom had a vagotomy in addition to the gastrectomy. Compared to vagotomy alone, there was no improvement in the recurrence rate which was 15 with recurrent ulcer, five with suspected recurrent ulcer, but there was a higher death rate. Six of the 71 patients died as a result of complications of the gastrectomy.

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* Eli Lilly and Co.

A study of the literature confirms our views on the treatment of this group of ulcers The death rate following vagotomy alone as a treatment for post-partial gastrectomy anastomotic ulcers is less than 1%, while no other current treatment is below 5% (Table 11). The recurrence rate on short-term follow-up is less than 16% and on long-term follow-up less than 19% (Table 12). Only vagotomy with partial gastrectomy has a lower

TABLE 8. *Treatment of the Complete Series of Anastomotic Ulcers Followed from one to 14 Years*

Antecedent Operation	Treatment of Anastomotic Ulcer	Related Death	Unrelated Death	I	II	IIIS	IIIU	IV	Recurrent Ulcer	Lost	Total
				(Visick Grade)							
BI	Med Rx	1	1	4	1	0	4	1	0	4	16
	2nd op—BI	0	0	0	0	0	1	0	0	0	1
	—BII	2	2	2	2	2	0	1	4	3	18
	—Vag	0	0	3	4	2	0	0	0	2	11
	—V & PG	0	2	2	3	0	1	0	0	1	9
	—Other	0	0	0	0	0	0	0	1	0	1
	Total	3	5	11	10	4	6	2	5	10	56
BII	Med Rx	2	6	11	8	1	3	1	0	14	46
	2nd op—BI	0	0	0	0	0	0	0	1	0	1
	—BII	2	1	4	0	2	1	0	7	1	18
	—Vag	0	4	15	9	3	6	1	7	15	60
	—V & O	0	0	4	2	1	1	0	1	1	10
	—V & PG	2	1	14	3	1	1	0	3	6	31
	—Other	0	0	0	1	0	0	0	3	1	5
	Total	6	12	48	23	8	12	2	22	38	171
V & Pyl	Med Rx	0	1	5	3	2	0	0	0	2	13
	2nd op—BI	0	0	0	0	0	0	0	1	0	1
	—BII	0	1	4	3	0	1	0	3	1	13
	—Vag	0	0	2	1	0	0	0	1	1	5
	—V & O	0	0	0	0	0	0	0	0	0	0
	—V & PG	0	0	3	0	0	0	0	0	0	3
	—Other	0	0	0	0	0	0	0	0	1	1
	Total	0	2	14	7	2	1	0	5	5	36
V & G-E	Med Rx	0	3	0	0	0	0	0	0	0	3
	2nd op—BI	0	0	0	0	0	0	0	1	0	1
	—BII	0	1	3	0	0	0	0	1	0	5
	—V & PG	0	0	0	0	0	0	0	1	0	1
	—Other	0	0	0	0	0	0	0	0	1	1
	Total	0	4	3	0	0	0	0	3	1	11
V & PG	Med Rx	0	1	1	2	3	1	0	0	3	11
	2nd op—BII	0	1	2	1	1	0	0	3	1	9
	—Vag	0	1	2	1	2	0	0	0	1	7
	—V & O	0	0	1	0	0	0	0	0	0	1
	—V & PG	0	0	1	1	0	1	1	0	0	4
	—Other	0	0	4	0	0	0	0	0	0	4
	Total	0	3	11	5	6	2	1	3	5	36
G-E	Med Rx	7	6	0	0	1	1	0	0	4	19
	2nd op—BI	1	0	0	0	0	0	0	1	1	3
	—BII	2	10	6	1	1	0	0	17	8	45
	—Vag	0	0	0	0	1	0	0	2	0	3
	—V & O	0	0	2	2	1	0	0	0	0	5
	—V & PG	0	0	1	1	0	0	0	0	1	3
	—Other	1	0	0	0	0	0	0	1	0	2
	Total	11	16	9	4	4	1	0	21	14	80

Med Rx—Treated medically only
BI—Partial gastrectomy of the Billroth I type
BII—Partial gastrectomy of the Billroth II type
Vag—Vagotomy only
Vag & PG—Vagotomy combined with partial gastrectomy
O—Other operations (Non-definitive surgical procedures such as closure of perforation, undersewing of bleeding vessel, laparotomy, any excision or take-down of anastomosis)
Related deaths—Those occuring in the immediate postoperative period or, when following medical treatment, caused by complications of a persistent ulcer
Unrelated deaths—From causes unrelated to the ulcer or its surgical or medical treatment

recurrence rate than this and that is only on short-term follow-up.

Exceptionally, additional surgery may be required. Only six of our patients required excision of the retained antra in the duodenal stump and every effort should be made to exclude this condition pre-operatively rather than subject the patient to unnecessary exploration. Stenosis of the anastomosis is rare, but this may require treatment by excision and reconstitution of the anastomosis.

Post-Gastroenterostomy Anastomotic Ulcer

This group should be treated by two-thirds partial gastrectomy. Our results for all forms of treatment were unsatisfactory in this group of patients. Forty-eight patients were treated with two-thirds partial gastrectomy and three died. The cause of death in these three patients was, however, from embolism in two and pneumonia in the other, and we feel that this is more a reflection on the age and debility of the patients than on the choice of operation. The recurrence was high, with 18 patients having a proven recurrent ulcer and none suspected of recurrence. Only eight patients were treated by vagotomy, but five of these required some reconstruction of the anastomosis. There were no deaths but two patients developed recurrent ulcers (Table 8). Our views agree with those in the literature. The mortality rate for partial gastrectomy is the same as that following vagotomy for post-gastroenterostomy ulcers (Table 13). The rate of ulcer recurrence following partial gastrectomy is less than half that of vagotomy alone in that group (Table 13 and 14). Curiously, the addition of vagotomy to the gastrectomy in post-gastroenterostomy ulcers appears to result in an increased operative mortality in the literature, although we ourselves have had no deaths in this group in our study.

TABLE 9. *Late Results of Treatment of Anastomotic Ulcer, Including Only the Patients Followed for Six Years or More*

Antecedent Operation	Treatment of Anastomotic Ulcer	Related Death	Unrelated Death	I	II	IIIS	IIIU	IV	Recurrent Ulcer	Lost	Total
					(Visick Grade)						
BI	Med Rx	1	0	2	1	0	4	1	0	1	10
	2nd op—BI	0	0	0	0	0	1	0	0	0	1
	—BII	0	0	2	1	1	0	1	2	2	9
	—Vag	0	0	2	0	0	0	0	0	0	2
	—V & PG	0	0	0	1	0	0	0	0	0	1
	Total	1	0	6	3	1	5	2	2	3	23
BII	Med Rx	1	3	8	8	1	2	1	0	4	28
	2nd op—BI	0	0	0	0	0	0	0	1	0	1
	—BII	0	0	3	0	1	0	0	4	0	8
	—Vag	0	0	5	3	0	2	0	5	3	18
	—V & O	0	0	2	0	0	0	0	1	0	3
	—V & PG	1	1	6	1	1	1	0	3	0	14
	—Other	0	0	0	0	0	0	0	3	0	3
	Total	2	4	24	12	3	5	1	17	7	75
V & Pyl	Med Rx	0	0	1	1	0	0	0	0	0	2
	2nd op—BII	0	0	0	0	0	1	0	1	0	2
	Total	0	0	1	1	0	1	0	1	0	4
V & G-E	Med Rx	0	1	0	0	0	0	0	0	0	1
	2nd op—BI	0	0	0	0	0	0	0	1	0	1
	—BII	0	0	2	0	0	0	0	0	0	2
	Total	0	1	2	0	0	0	0	1	0	4
V & PG	Med Rx	0	1	0	1	2	1	0	0	0	5
	2nd op—BII	0	1	1	1	0	0	0	3	0	6
	—V & PG	0	0	0	0	0	1	0	0	0	1
	—Vag	0	0	1	1	0	0	0	0	0	2
	—Other	0	0	2	0	0	0	0	0	0	2
	Total	0	2	4	3	2	2	0	3	0	16
G-E	Med Rx	6	3	0	0	0	1	0	0	3	13
	2nd op—BI	0	0	0	0	0	0	0	1	0	1
	—BII	1	2	6	0	1	0	0	13	2	25
	—Vag	0	0	0	0	1	0	0	0	0	1
	—V & O	0	0	2	0	0	0	0	0	0	2
	—V & PG	0	0	0	0	0	0	0	0	1	1
	—Other	0	0	0	0	0	0	0	1	0	1
	Total	7	5	8	0	2	1	0	15	6	44

TABLE 10. *Deaths due to Operation or Ulcer*

A. Immediate Post-operative Deaths (10 Patients)

Age (Years)	Antecedent Operation (s)	Operation for Anastomotic ulcer	Cause of Death	Contributing Cause
71	BI	BII	Duodenal fistula	None
70	BI	BII	Anastomotic dehiscence	None
45	BI & BII	V & PG	Peritonitis	None
75	BII	BII	Cardiac arrest	Long operation
55	BII	V & PG	Anastomotic dehiscence	None
67	G-E	BI	Pneumonia	Emergency operation for haemorrhage
53	G-E	BII	Pulmonary embolus	None
70	G-E	Closure	Cardiac arrest	Perforated ulcer, 18 hours
69	G-E & BII	BII	Anastomotic dehiscence	Perforated ulcer
71	G-E	BII	Pulmonary embolus	None

B. Late Deaths (10 Patients)

Age (Years)	Antecedent Operation (s)	Treatment	Interval from antecedent Operation to death (years)	Cause of Death
49	BI	Medical	1	Haemorrhage
81	BII	Medical	4	Haemorrhage
75	G-E	Medical	10	Haemorrhage
79	G-E	Medical	37	G-J-C fistula
74	G-E	Medical	22	Haemorrhage
63	G-E	Medical	27	Haemorrhage
70	G-E	Medical	32	Haemorrhage
78	G-E & BII	Medical	3	Haemorrhage
72	G-E	Medical	20	Haemorrhage
76	G-E	Medical	29	Haemorrhage

The cause of death in those treated medically was haemorrhage, except for one patient with a gastro-jejunocolic (GJC) fistula.

Treatment of Post-Vagotomy and Drainage of Anastomotic Ulcers

We would suggest repeat transabdominal vagotomy alone for this group. This is probably the most difficult group to make a decision on as such small numbers are involved in our study and in other series. Five patients were treated with vagotomy in our study and there were no deaths and one recurrence on short-term follow-up. Of 20 patients treated with partial gastrectomy, there were no deaths but six patients developed recurrent ulcers on short-term follow-up.

Review of the literature confirms that vagotomy is the operation of choice. There was a mortality rate of one percent following vagotomy and the recurrence rate was approximately 26% on short-term follow-up (Table 15). Following partial gastrectomy, the death rate was 6% and the recurrence rate 24%.

Two-thirds of the deaths following gastrectomy were in the post-vagotomy and pyloroplasty group, although less than half of the patients had had a vagotomy and pyloroplasty. This would tend to indicate that gastrectomy is particularly dangerous as a treatment for post-vagotomy and pyloroplasty anastomotic ulcers. The mortality rate in the literature of gastrectomy for ulcer following vagotomy with pyloroplasty is 9% (six deaths in 63 procedures). This high death rate may be caused by the difficulty in closing the duodenal stump in patients who have a pyloroplasty and a recurrent ulcer. As most of the pyloroplasties in the literature were of the Heineke Mikulicz type, a Finney or Jaboulay pyloroplasty may have an even higher mortality when a gastrectomy is carried out as a second operation.

Experience of anastomotic ulcer following vagotomy and drainage is at the present time limited, but we would expect as found by Fawcett and his colleagues,[9] that the success rate of vagotomy would be much lower in this group of recurrent ulcers than when vagotomy was carried out for primary peptic ulcer. We feel it is wrong, however, to suggest gastrectomy as a routine procedure for ulcers following vagotomy and drainage because gastrectomy is attended by an increased mortality rate and also because there is no advantage to be shown for gastrectomy in terms of prevention of ulcer recurrence compared with vagotomy. In a patient in whom satisfactory closure of the duodenal stump could be assured, it would be logical to suggest vagotomy and gastrectomy, but if these conditions cannot be met our first choice would remain vagotomy alone. Jejunal, stomal, or gastric ulceration after gastroenterostomy with vagotomy may meet these conditions. The mortality rate in the literature is 4% (three deaths out of 77 patients) for gastrectomy for recurrent ulcer following vagotomy with gastroenterostomy, but it might be possible to reduce this mortality by selection of patients with easily closed duodenal stumps.

TABLE 11. *Summary of the Literature Regarding the Results of Treatment of Post Partial Gastrectomy Ulcer*

Operation	Result	Present Study	Literature	Total Per cent
More proximal Gastrectomy	Excellent	15 (30)	98 (143)	65.3
	Recurrent Ulcer	12 (30)	40 (143)	30.1
	Dead	4 (38)	10 (161)	7.0
Vagotomy alone	Excellent	40 (54)	215 (291)	73.9
	Recurrent Ulcer	7 (54)	47 (291)	15.7
	Dead	0 (71)	3 (301)	0.8
Vagotomy and Other	Excellent	7 (9)	1 (3)	—
	Recurrent Ulcer	1 (9)	0 (3)	—
	Dead	0 (10)	0 (3)	—
Vagotomy and Partial Gastrectomy	Excellent	26 (31)	66 (86)	78.6
	Recurrent Ulcer	3 (31)	11 (86)	12.0
	Dead	2 (40)	5 (94)	5.2
Other	Excellent	1 (5)	4 (14)	—
	Recurrent Ulcer	4 (5)	9 (14)	—
	Dead	0 (6)	3 (16)	—
Medical Treatment	Excellent	32 (41)	16 (36)	62.3
	Recurrent Ulcer	9 (41)	20 (36)	37.7
	Dead	3 (62)	2 (35)	5.2

Note: Lost patients are included in the operative mortality statistics, but excluded from all other statistics in this and subsequent tables. Patients who died of unrelated causes are included as excellent results if the treatment controlled their ulcer disease and if ulcer disease did not contribute to their deaths.

Follow-up period varied 0–16 years. [1–4,7,8,12,13,15–18,21,22,24,28–30]

Figures in parentheses are the number of patients in each group.

Post-Vagotomy and Partial Gastrectomy

We recommend repeat transabdominal vagotomy in this group. It is essential to screen patients with ulcer following vagotomy with gastrectomy for ulcer diathesis due to endocrine tumours or retained antrum in the duodenum. Although none of our patients had a non-beta cell tumour of the pancreas, nor a parathyroid tumour, two of our 36 patients had retained antra in the duodenal stump. In both patients excision of the antral tissue (with more proximal gastrectomy in one) cured the ulcers. It has been the experience of others too that this group of patients tends to have an appreciable incidence of high gastrin-secreting or parathormone-secreting conditions. Of 12 patients with ulceration after gastric resection and vagotomy, performed separately, Wychulis[30] found two patients with multiple endocrine adenomas. Of 14 patients with ulceration after gastric resection and vagotomy (ten were one stage and four were two stage procedures) Stuart[23] found two patients with the Zollinger-Ellison syndrome. Only 13 of 1600 patients with a one stage vagotomy and antrectomy procedure developed recurrent ulcers in Scott's[19] study, but three of the 13 had a Zollinger-Ellison syndrome. The Zollinger-Ellison syndrome requires a total gastrectomy to control the ulcer diathesis.

If an ulcer diathesis such as an endocrine adenoma or retained antrum can be excluded, it is our experience that the anastomotic ulcer following vagotomy with gastrectomy is a benign disease attended by no deaths and a low recurrence rate. Treatment by repeat vagotomy gave excellent results: there was no mortality, and six traced patients of the seven who had a vagotomy all had excellent results on follow-up. Study of the literature shows few reports of repeat vagotomy for this type of ulcer (Table 16) although Jaffe[11] had excellent results in the three patients who had vagotomy in his study.

Reresection gave worse results in our hands; three of the eight patients followed had ulcer recurrence. There are more reports available for this operation and these show a recurrence rate in line with our results.

Even medical treatment in 11 patients in our study gave reasonable results with only one of the eight patients

TABLE 12. *Results of Treatment of Post Partial Gastrectomy Ulcers in the Literature on Follow-up of Five Years or More*[1,3,13,18]

Operation	Result	Present Study	Literature	Total Per cent
More proximal Gastrectomy	Excellent	8 (17)	19 (27)	61.4
	Recurrent Ulcer	7 (17)	8 (27)	34.1
Vagotomy alone	Excellent	10 (17)	58 (71)	77.3
	Recurrent Ulcer	5 (17)	11 (71)	18.2
Vagotomy and Partial Gastrectomy	Excellent	10 (14)	— —	—
	Recurrent Ulcer	3 (14)	— —	—
Other	Excellent	0 (3)	0 (1)	—
	Recurrent Ulcer	3 (3)	1 (1)	—
Medical Treatment	Excellent	23 (31)	2 (9)	—
	Recurrent Ulcer	8 (31)	7 (9)	—

Figures in parentheses are the number of patients in each group.

followed having a suspected persistent ulcer. We do not, however, recommend medical treatment for the definitive treatment of this, or any other type of anastomotic ulcer at this time.

Repeat vagotomy with more proximal gastrectomy was carried out in four patients, and excellent results were found in two on follow-up, with unsatisfactory results in the other two, although there were no proven recurrences. We feel that more proximal gastrectomy adds little to revagotomy for this type of ulcer. If there is no ulcer diathesis, more proximal gastrectomy is probably unnecessary and adds additional risk for no proven gain. If there is an ulcer diathesis, then the operation is inadequate to control the disease.

Deaths

Sixty-two patients are known to have died. All the ten patients who died in the immediate post-operative period had an autopsy, and in many cases autopsy was carried out in those who died of incidental causes. Autopsy information on the cause of death and the presence or absence of stomal ulceration is available in 41 of the 62 patients. Forty patients died of incidental causes and are judged to have good results following their gastric surgery since no evidence of recurrence was noted clinically or at autopsy in these patients, and their gastric surgery was adequate to last them until the end of their natural life span.

TABLE 13. *Summary of the Literature Regarding the Results of Treatment of Post Simple Gastroenterostomy Ulcers*[1–4,7,8,11,13,15–18,21,22,24,28–30] *(Follow-up Period 0–16 Years)*

Operation	Result	Present Study	Literature	Total Per cent
Partial Gastrectomy	Excellent	18 (36)	543 (664)*	80.1
	Recurrent Ulcer	18 (36)	98 (664)	16.6
	Dead	3 (48)	18 (773)	2.7
Vagotomy alone	Excellent	1 (3)	51 (87)	57.8
	Recurrent Ulcer	2 (3)	34 (87)	40.0
	Dead	0 (3)	2 (85)	2.3
Vagotomy and Other	Excellent	5 (5)	0 (2)	—
	Recurrent Ulcer	0 (5)	2 (2)	—
	Dead	0 (5)	0 (2)	—
Vagotomy and Partial Gastrectomy	Excellent	2 (2)	25 (34)	75.0
	Recurrent Ulcer	0 (2)	4 (34)	11.1
	Dead	0 (3)	4 (38)	9.8
Other	Excellent	0 (1)	24 (102)	23.3
	Recurrent Ulcer	1 (1)	76 (102)	74.8
	Dead	1 (2)	14 (108)	13.6
Medical Treatment	Excellent	7 (15)	14 (81)	21.9
	Recurrent Ulcer	8 (15)	67 (81)	78.1
	Dead	7 (19)	11 (78)	18.6

* Three patients also had vagotomy.

Figures in parentheses are the number of patients in each group.

TABLE 14. *Summary ofthe Literature Regarding Results of Treatment of Post Gastroenterostomy Ulcers on Follow-up of Five Years or More*[1,13,13,18]

Operation	Result	Present Study	Literature	Total Per cent
Partial Gastrectomy	Excellent	9 (23)	184 (239)	73.6
	Recurrent Ulcer	14 (23)	55 (239)	26.4
Vagotomy alone	Excellent	1 (1)	10 (20)	—
	Recurrent Ulcer	0 (1)	10 (20)	—
Other	Excellent	0 (1)	14 (81)	17.1
	Recurrent Ulcer	1 (1)	67 (81)	82.9
Medical Treatment	Excellent	3 (10)	3 (36)	13.0
	Recurrent Ulcer	7 (10)	33 (36)	87.0

Figures in parentheses are the number of patients in each group

Post-operative Deaths

During the post-operative period seven patients died following a partial gastrectomy; two died following a partial gastrectomy with vagotomy and one died during closure of a neglected perforated jejunal ulcer. The cause of death following re-gastrectomy for a post-gastrectomy anastomotic ulcer differed from the cause of death following gastrectomy for a post-gastroenterostomy anastomotic ulcer. Of the six patients with post-gastrectomy ulcers, five died due to intra-abdominal sepsis and one died of cardiac arrest during a prolonged and difficult gastrectomy. On the other hand, the deaths in the three patients with post-gastroenterostomy ulcers were due to pulmonary embolus in two and pneumonia in one, the anastomosis being sound in all these patients. This would confirm the clinical impression that in stomal ulcer patients gastrectomy is much more difficult technically in a patient with a previous gastrectomy.

Late Deaths

All these ten patients were on medical treatment. We found that these patients had died of complications of anastomotic ulcer, six months to seven years after treat-

TABLE 15. *Summary of the Literature Regarding the Results of Treatment of Post Vagotomy with Drainage*[8,9,11,12,17,20–23,30] *(Follow-up Period 0–16 Years)*

Operation	Result	Present Study	Literature	Total Per cent
Partial Gastrectomy	Excellent	12 (19)	56 (82)	67.3
	Recurrent Ulcer	6 (19)	18 (82)	23.8
	Dead	0 (20)	9* (123)	6.3
Vagotomy alone	Excellent	3 (4)	44 (65)	68.1
	Recurrent Ulcer	1 (4)	17 (65)	26.1
	Dead	0 (15)	1 (88)	1.1
Vagotomy and Other	Excellent	—	1 (1)	—
	Recurrent Ulcer	—	0 (1)	—
	Dead	—	0 (4)	—
Vagotomy and Partial Gastrectomy	Excellent	3 (4)	2 (2)	—
	Recurrent Ulcer	1 (4)	0 (2)	—
	Dead	0 (4)	0 (2)	—
Other	Excellent	—	2 (2)	—
	Recurrent Ulcer	—	0 (2)	—
	Dead	0 (1)	0 (11)	—
Medical Treatment	Excellent	14 (14)†	3 (11)	—
	Recurrent Ulcer	0 (14)	8 (11)	—
	Dead	0 (14)	0 (11)	—

* Six of these deaths followed vagotomy with pyloroplasty ulcers. The mortality rate for gastrectomy was 9.5 per cent if a pyloroplasty was the drainage procedure, and 3.9 per cent if gastroenterostomy was the drainage operation.

† Three dead of related causes.

Figures in parentheses are the number of patients in each group.

ment of their anastomotic ulcer. In all of these a clear history of anastomotic ulcer symptoms was available, and medical treatment was employed with varying degrees of vigour. At the time of initial assessment, the clinicians chose medical treatment either because the clinical diagnosis was not supported by barium meal examination, or because of the advanced age of the patients.

In one further patient an unhealed anastomotic ulcer was found at autopsy, but this had not contributed to the patient's death of pulmonary edema at the age of 86 years.

Summary

Three hundred and thirty-one patients were treated for 390 episodes of anastomotic ulceration at two Vancouver hospitals. These patients were followed and the recurrence rate after varying treatment for their anastomotic ulceration was evaluated in terms of mortality and recurrence rate. The overall death rate from ulcer or its treatment was 6% of the 331 patients, and 15% had a further ulcer recurrence after surgical treatment. After surgical treatment of the second anastomotic ulcer, 12% of that group went on to develop a third ulcer. One patient developed a fourth and fifth anastomotic ulcer.

Barium meal was effective in diagnosing 51% of the 321 anastomotic ulcers in which this examination was carried out. Peak acid output studies were most useful in the post-gastrectomy with or without vagotomy groups: a level of over 12 mEq. was diagnostic of hypersecretion and was present in 40% of these anastomotic ulcers. Gastroscopy gave a positive result in only 33% of the 72 instances in which it was employed; this was in the pre-fiber-optic era.

TABLE 16. *Summary of the Literature Regarding Results of Treatment of Post Vagotomy with Gastrectomy Ulcers*[2,11,21–23,30] *(Follow-up Period 0–16 Years)*

Operation	Result	Present Study	Literature	Total
Partial Gastrectomy	Excellent	5 (8)	14 (26)	19 (34)
	Recurrent Ulcer	3 (8)	8 (26)	11 (34)
	Dead	0 (9)	1 (28)	1 (37)
Vagotomy alone	Excellent	6 (6)	3 (3)	9 (9)
	Recurrent Ulcer	0 (6)	0 (3)	0 (9)
	Dead	0 (7)	1 (4)	1 (11)
Vagotomy and Other	Excellent	1 (1)	—	1 (1)
	Recurrent Ulcer	0 (1)	—	0 (1)
	Dead	0 (1)	—	0 (1)
Vagotomy and Partial Gastrectomy	Excellent	2 (4)	1 (1)	3 (5)
	Recurrent Ulcer	0 (4)	0 (1)	0 (5)
	Dead	0 (4)	0 (2)	0 (6)
Other	Excellent	4 (4)	—	4 (4)
	Recurrent Ulcer	0 (4)	—	0 (4)
	Dead	0 (4)	1 (1)	1 (5)
Medical Treatment	Excellent	7 (8)	—	7 (8)
	Recurrent Ulcer	1 (8)	—	1 (8)
	Dead	0 (11)	—	0 (11)

Figures in parentheses are the number of patients in each group.

Of the patients with anastomotic ulcer, 74% had prandial pain and 56% had one or more episodes of haemorrhage. Perforation of an anastomotic ulcer was present in 5%, 9% had obstructive symptoms and 2% had gastro-jejuno-colic fistulae. We found no patients with secreting tumours of the pancreas or parathyroid. Of 140 Billroth II anastomotic ulcers, 6% had retained antrum in the duodenal stump.

After comparison of the mortality and recurrence rate of the various treatment options available in this and other studies, we conclude that vagotomy is the treatment of choice for post-gastrectomy anastomotic ulcer, for post-vagotomy and drainage anastomotic ulcer and for post-gastrectomy with vagotomy anastomotic ulcer. We also conclude that partial gastrectomy alone is the treatment of choice for post-gastroenterostomy anastomotic ulcer.

References

1. Andros, G., Donaldson, G. A., Hedberg, S. E. and Welch, C. E.: Anastomotic Ulcers. Ann. Surg., **165**:955, 1967.
2. Balint, J. A., Cooper, G. W., Price, E. C. V., Pulvertaft, C. N. and Swynnerton, B. F. A.: The Management of Anastomotic Ulcer. Lancet, **1**:55, 1957.
3. Beal, J. M.: The Surgical Treatment of Marginal Ulcer. Amer. Surg., **25**:1, 1959.
4. Boles, R. S., Marshall, S. F. and Bersoux, R. V.: Follow-up Study of 127 Patients with Stomal Ulcer. Gastroenterology, **38**:763, 1960.
5. Braun, H.: Demonstration Eines Praparetes Einer 1 Monate Nach der Ausfuhrung der Gastro-Enterostomie Entstandeden Perforation des Jejunum. Verh. Ges. Chir., **28**:94, 1899.
6. Cleator, I. G. M., Thompson, C. G., Sircus, W. and Combes, M.: Bioassay Evidence of Abnormal Secretin-like and Gastrin-like Activity in Tumour and in Blood in Cases of Choleraic Diarrhoea. Gut, **11**:206, 1970.
7. Edwards, L .W., Herrington, J. L. Jr., Cate, W. R. Jr., *et al:* Gastrojejunal Ulcer: Problems in Surgical Management. Ann. Surg., **143**:235, 1956.
8. Everson, T. C. and Allen, M. J.: Gastrojejunal Ulceration. A.M.A. Arch. Surg., **69**:140, 1954.
9. Fawcett, A. N., Johnston, D. and Duthie, H. L.: Vagotomy for Recurrent Ulcer After Vagotomy and Drainage for Duodenal Ulcer. Brit. J. Surg., **56**:111, 1969.
10. Goligher, J. C.: The Comparitive Results of Different Operations in the Elective Treatment of Duodenal Ulcer. Brit J. Surg., **57**:780, 1970.
11. Jaffe, B. M., Newton, W. T., Judd, D. R. and Ballinger, W. F.: Surgical Management of Recurrent Peptic Ulcers. Amer. J. Surg., **117**:214, 1969.
12. Judd, D. R., Starkloff, G. B., Morioka, W., *et al.*: Vagotomy and Drainage Procedures. Arch. Surg., **102**:242, 1971.
13. Knox, W. G. and West, J. P.: Vagus Section in the Treatment of Gastrojejunal Ulcer. Ann. Surg., **149**:481, 1959.
14. McGuigan, J. E. and Trudeau, W. C.: Immunochemical Measurement of Elevated Levels of Gastrin in the Serum of Patients with Pancreatic Tumours of the Zollinger-Ellison Variety. N. Engl. J. Med., **278**:1308, 1968.
15. Marshall, S. F. and Terrell, G. K.: Postoperative Recurrent Ulcer. Surg. Clin. N. Amer., 37:653, 1957.
16. Osnes, S. V.: Transthoracic Resection of Vagi in the Treatment of Gastrojejunal Ulcer. Acta Chir. Scand., **110**:373, 1956.
17. Postlethwait, R. W.: Results of Surgery for Peptic Ulcer. Philadelphia and London, W. B. Saunders Co., 1963.
18. Priestley, J. T. and Gibson, R. H.: Gastrojejunal Ulcer: Clinical Features and Late Results. Arch. Surg., **56**:625, 1948.
19. Scott, H. W., Sawyers, J. F., Gobbel, W. G., Herrington, J. L., Edwards, W. H. and Edwards, L. W.: Vagotomy and Antrectomy in Surgical Treatment of Duodenal Ulcer Disease. J. Clin. North America, **46**:349, 1966.
20. Shiffman, M. A.: Evaluation of Recurrence Following Vagotomy and Pyloroplasty. Int. Surg., **48**:574, 1967.
21. Small, W. P.: The Recurrence of Ulceration After Surgery for Duodenal Ulcer. J. Roy. Col. Surg., Edinb., **9**:255, 1964.
22. Small, W. P., Smith, A. N., Ruckley, C. V., Falconer, C W. A., Sircus, W, McManus, J. P. A. and Bruce, J.: The Continuing Problem of Jejunal Ulcer. Amer. J. Surg., **121**:541 1971.
23. Stuart, M. and Hoerr, S. O.: Recurrent Peptic Ulcer Following Primary Operations with Vagotomy for Duodenal Ulcer. Arch. Surg., **103**: 129, 1971.
24. Thompson, J. E.: Stomal Ulceration after Gastric Surgery. Ann. Surg., **143**:697, 1956.
25. Thomson, C., Cleator, I. G. M. and Sircus, W.: Experiences with a Rat Bioassay in the Diagnosis of the Zollinger-Ellison Syndrome. Gut, **11**:409, 1970.
26. Visick, A. H.: A Study of the Failures After Gastrectomy. Ann. R. Coll. Surg., **3**:266, 1948.
27. Walter, W., Chance, D. P. and Berkson, J.: A Comparison of Vagotomy and Gastric Resection for Gastro-Jejunal Ulceration: A Follow-up Study of 301 Cases. Surg. Gynecol. Obstet., **100**:1, 1955.
28. Wells, B. W.: Result of Vagotomy in Treatment of Anastomotic Ulcer. Lancet, **1**:598, 1954.
29. Wells, C. and Silberman, R.: Transthoracic Vagotomy for Stomal Ulceration. Lancet, **1**:406, 1960.
30. Wychulis, A. R., Priestley, J. T. and Foulk, W. T.: A Study of 360 Patients with Gastrojejunal Ulceration. Surg. Gynecol. Obstet., **122**:89, 1966.

Infection in the Severely Traumatized Patient

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HOSPITAL-ACQUIRED INFECTION has become increasingly prevalent, especially in those patients whose severe underlying disease is ameliorated by modern medical therapy.[1–5] Infection is common and a frequent cause of death in acute leukemia,[6,17] Hodgkin's disease,[8] and renal or cardiac transplantation.[9,10] These infections are usually hospital-acquired and are caused by organisms generally considered to have low virulence (e.g., *Pseudomonas aeruginosa*) or by organisms frequently associated with the normal flora of the mouth and colon (e.g., *E. coli* or *Candida albicans*).[11–14] The association of nosocomial infection with specific predisposing factors such as corticosteroids,[15] broad spectrum antibiotics,[4,16,17] indwelling urinary or venous catheters,[18–21] cancer chemotherapeutic or immunosuppressive agents,[6–13,15] multiple transfusions,[22–24] tracheostomies,[25] contaminated water,[26] respirators,[27,28] disinfectants,[29] humidifiers,[30] and intravenous tubing or preparations[31] is well documented. There is a relationship between the severity of illness and pharyngeal colonization with gram negative bacilli.[32] Potential pathogens are acquired by patients in various hospital settings. For example, acquisition of *Klebsiella* by the intestinal flora following admission to a general hospital led to a high incidence of later klebsiella infection.[33] *Pseudomonas aeruginosa* is frequently acquired by patients hospitalized in specialized cancer therapy centers;[8,10] pseudomonas bacteremia in such hospitals occurs primarily in the colonized patient.[6] The route by which patients come in contact with pathogens is seldom established, although contamination via water supplies, the local environment, and patient to staff or patient contact are believed largely responsible.[25,33–35] In a study of tracheostomy colonization by *Pseudomonas aeruginosa*, it was found that on admission the patients did not have bacterial colonization in their stool or elsewhere but that *Pseudomonas aeruginosa* was carried to the patient by various means, notably the hands of attending personnel.[25]

It had been apparent at the Center for the Study of Trauma (CST) of the University of Maryland that infection occurred frequently and was a major cause of death following severe trauma in patients admitted to the CST. In this connection the relations between bacterial infection and hemorrhagic shock described by Schweinburg, Frank, and Fine[37] should be recalled. A review of all records from the microbiology laboratory over a one-year period revealed 90 nosocomial infections in 135 patients hospitalized for more than 2 days while none were noted in 94 patients remaining for less than 2 days.[36] During that year, 35 bacteremias, 8 wound infections, 40 urinary tract infections, and 7 peritoneal infections occurred. The most prevalent organisms, in decreased order of frequency, included: *Pseudomonas* (24%), *Candida* (16%), *Klebsiella* (10%), *Enterobacter* (8%), *E. coli* (6%) and coagulase negative *Staphylococcus* (6%). However, nearly 50% of the bacteremias were caused by organisms of low virulence such as *Candida*, coagulase-negative *Staphylococcus, Herellea, Serratia*, Mima, etc. Like the patient with severe but chronic underlying illness, the traumatized patient apparently has a loss of many host defense mechanisms, thus predisposing him to infection with organisms of low virulence which, after becoming part of the endogenous

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flora, gain access to the patient via the multiple invasive procedures (such as tracheostomy and indwelling catheters) necessary for his management. This retrospective investigation clearly documented the high incidence of nosocomial infection in the CST and pointed to the necessity for a prospective evaluation of all patients admitted; the study to consider clinical signs and symptoms of infection, microbiological documentation of each suspected infection, and an evaluation of the factors which predisposed the individual trauma patient to subsequent infection in this setting. The present report is concerned with the incidence of nosocomial infections in severely traumatized patients, the specific factors predisposing to these infections, and the means by which potential pathogens initially reach the patient.

Methods

Nosocomial infections are those infections which develop clinically and bacteriologically in hospitalized patients in whom the infection was neither present nor incubating at the time of admission.

From September 27 to November 20, 1971, each patient admitted to the CST was seen daily and examined for evidence of infection. In addition, daily records were maintained indicating the use of endotracheal tubes, tracheotomy, respirators (volume controlled), oxygen, nasogastric tubes, arterial and/or venous catheters (including dates of insertion and withdrawal), indwelling urinary catheters, prophylactic and therapeutic antibiotics, and corticosteroids. Notation was made of any prior underlying illness such as diabetes, chronic lung disease, or cardiac failure which might be expected to predispose to infection. While in the Unit, patients were observed for central nervous system depression, pulmonary shunting, congestive heart failure, and renal failure.

Most patients are admitted directly from the scene of trauma or following brief emergency care at another hospital. Occasionally, patients from other parts of this hospital who have developed refractory shock are transferred to the CST. Patients undergoing cardiac or major thoracic surgery are transferred to the CST for the first 1–3 days of postoperative care. Each patient admitted was observed as noted above but only those admitted as "shock-trauma" patients are considered in this report. The CST is a self-contained integrated unit constructed specifically for the therapy and study of severely injured patients. The patient care area consists of a central nursing station surrounded by 12 open-ended cubicles containing a bed, sink, biomedical monitoring equipment, and space for ventilators or other equipment. The physicians and nurses assigned to the CST have no other hospital commitments; however, consultants from a number of other areas provide their services. The staff don either scrub suit or gown upon entering and are encouraged to wash their hands in betadine solution which is kept at each bedside. All indwelling urinary catheters are attached to closed drainage and are opened only to obtain urine cultures. Indwelling venous and arterial catheters are inserted with sterile technique; and the skin site is cleaned before a new dressing is applied each day the catheter remains in place. Volume controlled respirators are sterilized between patient usage and the respirator and parenteral fluid tubing to each patient is replaced daily.

Patients are discharged to other areas in the hospital as soon as their need for specialized trauma care ceases. For the purpose of this report, infections and deaths ocurring after transfer out of the CST have not been considered.

TABLE 1. *Shock Trauma Unit, University of Maryland, September 27-November 20, 1971*

Admissions	62
≥ 5 days	25
Infections	
On Admission	6
Nosocomial	19
Deaths	
<5 Days	5(0)
≥ 5 Days	4(3)

( ) Death from infection.

Results

Patient Population

Sixty-two "shock trauma" patients were admitted during the 55 days of study (Table 1). The length of stay was arbitrarily divided into A) less than five days, i.e., those patients whose trauma was so severe that they died rapidly despite all attempts at therapy or those patients with less severe trauma who were either discharged to home or transferred to other parts of the hospital and B) five or more days, i.e., those patients with intermediately severe trauma who required prolonged intensive care. Six patients had infections (either apparent or incubating) on admission (Table 2) and 15 patients developed 19 nosocomial infections. There were four deaths among the 25 patients in group B; three of the four died of nosocomial infection.

Table 3 lists the site, etiologic organism, and the number of days after admission when the infection was first detected for each of these nosocomial infections. The eight patients with urinary tract infection ($>$ 100,000 colonies/cc of each organism following at least one prior sterile urine culture) occurred in association with an indwelling urinary catheter inserted on admission. The three pneumonias occurred on days 4, 4, and 5 following

TABLE 2. *Infections on Admission**

Site	Organism	Related Factors
Ileitis	*Enterobacter* sp†	Adhesions following appendectomy
Sinusitis	Mucormycosis and *Candida albicans*	Diabetic ketoacidosis and tooth extraction
Pelvic wound	*Bacteroides* sp and multiple gram negative bacilli	Radical pelvic surgery for cervical carcinoma
Abdominal wound	*Bacteroides* sp†	Shotgun wound to abdomen
Enterocolitis	*Pseudomonas aeruginosa*† and *Proteus mirabilis*	Renal transplant with immunosuppression
Neck wound	*Staphylococcus epidermidis*	Tracheal and esophageal transection in accident

* Apparent or incubating on admission.
† Bacteremia

tracheostomy and days 4, 5, and 5 of continuous volume controlled respirator use.

All of these patients had severe chest trauma with lung contusions and one patient also had severe preexisting emphysema.

The patient with purulent sinusitis suffered previously from an upper respiratory tract viral infection before the auto accident which severed his trachea and esophagus and produced a *Staphylococcal epidermidis* bacteremia (i.e., two separate positive blood cultures in association with fever and chills). One patient with *Enterobacter* sp. ileitis upon admission later developed an *E. coli* peritonitis with sepsis and death. The other patient with peritonitis was diagnosed clinically (while the patient was receiving cephalothin) but had negative blood cultures; and responded to chloramphenicol therapy. One patient with an extensive comminuted femoral fracture developed a severe wound infection while receiving cephalothin.

TABLE 3. *Nosocomial Infections*

Site	Organism	Days Following Admission
Urinary Tract Infection	*E. coli*	7
Urinary Tract Infection	*Klebsiella* sp and *Pseudomonas aeruginosa*	12
Urinary Tract Infection	*E. coli* and *Pseudomonas aeruginosa*	21
Urinary Tract Infection	Group D *Streptococcus*	1
Urinary Tract Infection	*Candida albicans*	10
Urinary Tract Infection	Alpha *Streptococcus*	8
Urinary Tract Infection	*Staphylococcus epidermidis*	4
Urinary Tract Infection	*Staphylococcus epidermidis*	2
Pneumonia	*Pseudomonas aeruginoasa** and *Staphylococcus aureus*	5
Pneumonia	*Pseudomonas aeruginosa* and *Staphylococcus aureus*	5
Pneumonia	*Pseudomonas aeruginosa* and *Staphylococcus epidermidis**	4
Sinusitis	*Staphylococcus epidermidis*	3
Peritonitis	*E. coli**	9
Peritonitis	(none isolated).	3
Leg Wound	*Clostridia perfringens* and *Pseudomonas aeruginosa*	6
Catheter Related Bacteremia	*Enterobacter aerogenes**	4
Catheter Related Bacteremia	*Herellea* sp*	4
Catheter Related Bacteremia	*Serratia* sp*	10
Bacteremia, Origin Unknown	*Staphylococcus epidermidis**	1

* Bacteremia

Three patients had catheter-associated bacteremias; two occurred in patients who had both arterial and venous lines in place, the other occurred in a patient with only a venous catheter. The length of catheterization in these three patients was 4, 4, and 10 days. Finally, one patient with multiple extremity fractures, a pelvic fracture, and a flail chest, necessitating an endotracheal tube and respirator plus arterial, venous, and urinary catheters developed a *Staphylococcus epidermidis* bacteremia (as defined above) within one day of admission; the site of origin is not known although the venous catheter was suspected.

Gram negative bacilli (including *Pseudomonas aeruginosa* in six infections) were isolated in eleven of these 19 infections; *Staphylococcus aureus* was isolated twice. Seven of the 19 infections were associated with a bacteremia.

In most instances nosocomial infection occurred within the first week after admission to the CST. These infections appear 1) related to the degree of the initial trauma and/or its therapy, 2) caused by organisms acquired following admission to the CST, and 3) frequently progress to bacteremia despite the patient's good health before injury.

Predisposing Factors

The following prospective observations were made to determine the association between the severity of trauma, the length of hospitalization, and various therapeutic maneuvers with the later development of nosocomial infection.

The patients were divided into two groups (A and B) based on length of CST stay. Of the 37 patients (Table 4) who were in the Center for the Study of Trauma less

TABLE 4. *Length of Stay in Shock Trauma Unit*

	Total Patients	Patients with Infection (%)
4 Days or less	37	0 (0%)
5 Days or more	25	15* (60%)

* 19 nosocomial infections occurred in these 15 patients

than five days none developed infection, whereas 15 (60%) of the 25 patients in the CST for five or more days developed the 19 infections discussed above. Although some of the infections in the latter group occurred before the fifth day, all of these patients would have required prolonged CST care whether or not they had developed infection.

An arbitrary criterion of "severe trauma" showed similar results. Patients with 1) clinical shock on admission and/or 2) volume respirator use for at least the first 24 hours, and/or 3) mental obtundation or coma persisting at least 24 hours, and/or 4) fractures involving more than one extremity were classified as "severely traumatized." Fourteen (48%) of these 29 patients (Table 5) developed one or more nosocomial infections whereas only one (3%) of the 33 "less severely traumatized" patients developed such infection.

Because the five day limit clearly divided these patients into two distinct groups with respect to predisposition to infection, the following data has been considered only in regard to those 25 patients in the CST for five or more days.

The three pneumonias occurred among the 16 patients with tracheostomies. Although tracheostomy does afford potentially easy access to the tracheobronchial tree and may well be a major predisposing factor to pneumonia, each patient to develop pneumonia had severe existing lung pathology.

In this group of 25 patients, all but two had indwelling urinary catheters for periods of 3–31 days from admission with a mean time of 10.1 days and a median of 8.5 days. Eight (35%) of these 23 patients developed a urinary tract infection. There was no apparent cause (e.g., local trauma) for infection other than catheterization. Infection was first documented on days 1, 2, 4, 7, 8, 10, 11, and 12 respectively after insertion of the catheter.

"Prophylactic" systemic antibiotics (ampicillin—2, cephalothin—8, tetracycline—2, penicillin—2, methicillin—1) were given to fifteen patients, for fractures—11, "bronchitis"—1, abdominal surgery—1, and aspiration—2. Despite this rather widespread usage, the incidence of infection possibly related to the use of prophylactic systemic antibiotics (27%) did not differ from the incidence found without their use (30%). This suggests that factors other than antibiotics predispose to infection; however, antibiotics do encourage infections to be caused by more resistant organisms.[4]

Table 5. *Initial Status in Shock Trauma Unit*

	Total Patients	Patients with Infection (%)
Severe* Trauma	29	14 (48%)
Less Severe Trauma	33	1 (3%)

* Shock on admission, and/or respirator for at least 24 hours, and/or stupor or coma persisting at least 24 hours, and/or fractures involving more than one extremity.

Table 6. *Arterial and Venous Catheters and Infection**

Arterial Catheters	
Inserted	19 patients
Inserted >48 hrs.	19 patients
Range	3–18 days
Mean	8.4 days
Median	7 days
Venous Catheters	
Inserted	25 patients
Inserted >48 hrs.	10 patients
Range	5–11 days
Mean	6.9 days
Median	6.5 days
Catheter Related Infections	

Organism	Days From Insertion to Bacteremia	
	Arterial	Venous
Serratia sp.	10	10
Herellea sp.	—	4
Enterobacter aerogenes	4	4

* Includes only the 25 patients in the STU >5 days.

Corticosteroids were used in too few patients to allow meaningful comparisons.

It was difficult to prove an arterial or venous catheter as the cause or site of a bacteremia. In this study, we accepted a catheter as causative if it had been in place more than 48 hours, the culture was positive and there was no other primary site of infection after extensive examination, x-rays, and microbiologic studies. Using these criteria, there were three catheter-associated bacteremias. Table 6 indicates the number of patients with prolonged arterial and venous catheterization and the association with catheter-induced bacteremias.

Acquisition of Organisms

Three weeks before the prospective study began, a patient with pneumonia caused by a carbenicillin resistant *Pseudomonas aeruginosa* was transferred into the CST from the surgical service. During the next three weeks, six patients acquired a *Pseudomonas aeruginosa* with identical sensitivity patterns in cultures obtained from their tracheostomies; four developed pneumonia leading to death in three.

During this prospective study, cultures taken by deep aspiration were obtained almost daily on all patients with tracheostomies (Table 7). All 20 patients with tracheostomies (4 in group A and 16 in group B) acquired potential pathogens. Within 48 hours, an average of 1.5 pathogens per patient were acquired with an average of three pathogens per patient after five days of tracheostomy. The most commonly acquired organisms included *Pseudomonas aeruginosa*—14 patients, group D *Streptococcus* sp.—9, *Staphylococcus aureus*—8, and *Klebsiella* sp.—6.

TABLE 7. *Acquisition of Pathogens Following Tracheostomy*

Days Post Tracheostomy	0	1	2	3	4	5	6	7	8	9	10	10+
Newly Acquired Pathogens	10	19	5	4	6	6	0	5	4	1	1	6
Patients with Tracheostomy	20	19	17	17	14	13	13	12	10	9	8	7

Potential Pathogens	Patients Acquiring	Potential Pathogens	Patients Acquiring
Pseudomonas aeruginosa	14	*E. coli*	5
Group D Streptococcus sp.	9	*Serratia* sp.	4
Staphylococcus aureus	8	*Candida albicans*	4
Enterobacter sp.	7	*Proteus mirabilis*	4
Klebsiella sp.	6	*Herellea* sp	3

Undoubtedly some of these organisms were originally part of the patients endogenous flora. However, the finding of 14 of 20 patients with *Pseudomonas aeruginosa* (most were resistant to carbenicillin) suggests acquisition, because this organism is not frequently cultured from normal individuals, although the selective pressure of antibiotic administration may facilitate colonization as well as *in vitro* detection.[25] The exact means of acquisition are not known but the following observations in the CST suggest that considerable acquisition is via patient to personnel to patient contact: all staff members do not regularly wash before or after examining a patient; scrub suits or gowns are worn in the CST but are not changed when moving from cubicle to cubicle, rounds are conducted at the bedside with multiple physicians examining each patient, and certain examining equipment is common to all patients (e.g., stethoscopes and reflex hammer). Cultures of personnel (Table 8) frequently revealed potential pathogens and cultures of gowns and scrub suits often demonstrated contamination. Extensive environmental cultures (Table 9) suggest that despite some contaminated areas (sink, drain), the physical environment is relatively clean; these data suggest that personnel rather than the environment is the most likely source of pathogens.

Summary

These observations and our prior study[36] indicate that nosocomial infection in severely traumatized patients is a major cause of morbidity. Most infections occur in that group of patients who require prolonged intensive care because of very severe trauma. In this subgroup (group B), it is apparent that urinary catheters predispose to urinary tract infections; tracheostomies are associated with acquisition of potential pathogens and, in the patient with severe lung pathology, these organisms may lead to pneumonia; prolonged venous and/or arterial catheterization may lead to bacteremia.

The organisms causing these nosocomial infections include gram negative bacilli (e.g., *Pseudomonas aeruginosa* and *Klebsiella* sp.) plus other organisms of low virulence which often comprise the normal host's flora (e.g., *Staphylococcus epidermidis* and *Candida albicans*). Those organisms acquired during the period of intensive care were probably carried to the patient via the personnel whose hand cultures were often positive rather than via contaminated respirators, humidifiers or intravenous tubing, solutions, or blood products.[25,31,33,35] The frequent use of systemic antibiotics (both prophylactic and therapeutic) may have further tended toward colonization and superinfection by the more resistant endogenous and acquired organisms.[4]

This investigation suggests that a renewed emphasis be placed on reverse isolation[34] especially with regard to measures including adequate hand washing with a compound which destroys gram negative bacilli (e.g., betadine), separate gowns for each patient examined, and reduction of non-essential staff members from the patient cubicle area. Patients from elsewhere in the

TABLE 8. *Staff Cultures*

Hands (fingers pressed upon blood agar plates)

Physicians	6/14 had pathogens*
Nurses	4/13 had pathogens
Technicians	1/7 had pathogens

Wrist Bands (rodac plate imprints) of Gowns
>50 colonies isolated from 3/7
Waist Bands (rodac plate imprints) of Gowns
>50 colonies isolated from 3/8

* Gram negative bacilli and/or *Staphylococcus aureus*

TABLE 9. *Environmental Cultures*

Sink Drains
21/33 samples from 11 bedside sinks were contaminated with gram negative bacilli.
Klebsiella sp—13, *Pseudomonas aeruginosa*—8, *E. coli*—8, *Enterobacter* sp—9
Faucet
4/12 samples from 8 sinks were contaminated with gram negative bacilli.
Klebsiella sp—1, *Alcaligenes* sp—1, *Moraxella* sp—1, *Achromobacter* sp.—1
Counter Tops at Bedside
0-31 colonies/rodac plate, mostly *Bacillus* sp and *Staphylococcus epidermidis*
Hand Lotions
0/7 samples were contaminated.
Containers with Alcohol Soaked Sponges
2/7 contaminated with *Staphylococcus epidermidis*
Petroleum Jelly
1/1 contaminated with group D *Streptococcus* sp. and *Staphylococcus epidermidis*.
Respirator Tubing
2/35 samples contaminated with *Klebsiella* sp (same respirator, patient's tracheostomy previously colonized with *Klebsiella* sp)
Respirator Water Trap
0/13 samples contaminated with gram negative bacilli.
(4/13 with *Staphylococcus epidermidis* and 1/13 with Alpha *Streptococcus* sp.)
Heated Humidifiers
2/8 samples contaminated with *Moraxella* sp; one of these also contaminated with *Pseudomonas aeruginosa*.

hospital with known infection should be excluded from trauma units. Such a program must encompass not only nurses but consultant physicians, x-ray technicians, housekeepers, etc. and should be in conjunction with a policy prohibiting prolonged intravascular catheterization and discouraging excessive use of indwelling urinary catheters. Scrupulous aseptic technique when manipulating a tracheostomy is essential. The program must operate in conjunction with a routine method of bacterial surveillance of equipment (respirators, humidifiers, examining equipment, etc.) and water supplies.

The seriously traumatized patient must be recognized as one who has marked impairment of his normal host defenses and must, therefore, be treated with diligent efforts to prevent infection.

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References

1. Adler, J. L., Burke, J. P. and Finland, M.: Infection and Antibiotic Usage at Boston City Hospital, January 1970. Arch. Intern. Med., **127**:460, 1971.
2. Feingold, D. S.: Hospital-acquired Infections. New Engl. J. Med., **283**:1384, 1970.
3. Fekety, F. R., Jr.: Nosocomial Infections. Postgrad. Med., **50**:115, 1971.
4. Finland, M., Jones, W. F. and Barnes, M. W.: Occurrence of Serious Bacterial Infections since the Introduction of Antimicrobial Agents. JAMA, **170**:2188, 1959.
5. Rogers, D. E.: The Changing Pattern of Life-threatening Infections. New Engl. J. Med., **261**:677, 1959.
6. Schimpff, S., Young, V. and Greene, W.: Origin of Infection in Acute Nonlymphocytic Leukemia—Significance of Hospital Acquisition of Potential Pathogens. Ann. Int. Med., **77**:707, 1972.
7. Hersh, E. M., Body, G. P., Nies B. A., *et al.*: Causes of Death in Acute Leukemia: A Ten Year Study of 414 Patients from 1954–1963. JAMA, **193**:105, 1965.
8. Casazza, A. A., Duvall, C. P. and Carbone, P.: Summary of Infectious Complications Occurring in Patients with Hodgkin's Disease. Cancer Res., **26**:1290, 1966.
9. Cooley, D. A., Hallman, G. L., Liotta, D., Leachman, R. D. and Messmer, B. J.: Cardiac Replacement: Current Status of Cardiac Transplants and Prostheses. Ann. Int. Med. **73**: 677, 1970.
10. Editorial: Death after Transplantation. Am. J. Med. **42**:327, 1967.
11. Bodey, G. P.: Epidemiological Studies of *Pseudomonas* Species in Patients with Leukemia. Am. J. Med. Sci. **260**:82, 1970.
12. Schimpff, S. C., Moody, M. and Young, V. M.: Relationship of Colonization with Pseudomonas Bacteremia in Cancer Patients. Antimicrob Agents Chemother., **10**:240, 1970.
13. Schimpff, S., Satterlee, W., Young, V. M. and Serpick, A.: Empiric Therapy with Carbenicillin and Gentamicin for Febrile Patients With Cancer and Granulocytopenia. New Engl. J. Med **284**:1061, 1971.
14. Winterbauer, R. H., Turck, M. and Petersdorf, R. G.: Studies on the Epidemiology of *Escherichia coli* Infections. V. Factors Influencing Acquisition of Specific Serologic Groups. J. Clin. Invest., **46**:21, 1967.
15. Frenkel, J. K.: Role of Corticosteroids as Predisposing Factors in Fungal Diseases. Lab. Invest., **11**:1192, 1962.
16. Magarey, C. J., Chant, A. D. B., Rickford, C. R. K. and Margaray, J. R.: Peritoneal Drainage and Systemic Antibiotics after Appendicectomy. Lancet, **2**:179, 1971.
17. Price, D. J. E. and Sleigh, J. D.: Control of Infection Due to *Klebsiella aerogenes* in a Neurosurgical Unit by Withdrawal of all Antibiotics. Lancet, **2**:1213, 1970.
18. Collins, R. N., Braun, P. A., Zinner, S. H., *et al.*: Risk of Local and Systemic Infection with Polyethylene Intravenous Catheters. New Engl. J. Med., **279**:34, 1968.
19. Martin, C. M., Vaquer, F., Meyers, M. S. and El-Dadah, A.: Prevention of Gram Negative Rod Bacteremia Associated with Indwelling Urinary-tract Catheterization. Antimicrob Agents Chemother., 617, 1963.
20. Smits, H. and Freedman, L. R.: Prolonged Venous Catheterization as a Cause of Sepsis. New Engl. J. Med., **276**:1229, 1967.
21. Thornton, G. F., Lytton, B. and Andriole, V. T.: Bacteriuria During Indwelling Catheter Drainage. JAMA, **195**:179, 1966.
22. Blacklow, N. R., Watson, B. K., Miller, G. and Jacobson, B. M.: Mononucleosis with Heterophil Antibodies and EB Virus Infection. Acquisition by an Elderly Patient in Hospital. Am. J. Med., **51**:449, 1971.
23. Blumberg, B. S., Gerstley, B. J. S., London, W. T., Millman, I., Sutnick, A. I. and Zavatone, V.: Hepatitis Virus and Australia Antigen. J. Clin. Invest., **48**:9a, 1969.
24. Buchholz, D. H., Young, V. M., Friedman, N. R., Reilly, J. A. and Mardiney, M. R., Jr.: Bacterial Proliferation in Platelet Products Stored at Room Temperature: Transfusion-induced Enterobacter Sepsis. New Engl. J. Med., **285**: 429, 1971.
25. Lowbury, E. J., Thom, B. T., Lilly, H. A., *et al.*: Sources of Infection with *Pseudomonas aeruginosa* in Patients with Tracheostomy. J. Med. Microbiol., **3**:39, 1970.
26. Cross, D. F., Benchimol, A. and Dimond, E. G.: The Faucet Aerator—A Source of Pseudomonas Infection. New Engl. J. Med., **264**:1430, 1966.
26. Mertz, J. J., Scharer, L. and McClement, J. H.: A Hospital Outbreak of Klebsiella Pneumonia from Inhalation Therapy with Contaminated Aerosol Solutions. Amer. Rev. Resp. Dis., **95**:454, 1967.
28. Moffet, H. L. and Williams, T.: Bacteria Recovered from Distilled Water and Inhalation Therapy Equipment. Amer. J. Dis. Child., **114**:19, 1967.
29. Burdon, D. W. and Whitby, J. L.: Contamination of Hospital Disinfectants with *Pseudomonas* species. Brit. Med. J., **2**: 153, 1967.
30. Ringrose, R. E., McKnown, B., Felton, F. G., *et al.*: A Hospital Outbreak of *Serratia marcescens* Associated with Ultrasonic Nebulizers. Ann. Int. Med., **69**:719, 1968.
31. Nosocomial Bacteremias Associated with Intravenous Fluid Therapy—USA. U.S. Dept. of Health, Education, and Welfare, Epidemiologic Notes and Reports, Atlanta, Georgia, March 12, 1971.
32. Johanson, W. G., Pierce, A. K. and Sanford, J. P.: Changing Pharyngeal Bacterial Flora of Hospitalized Patients. New Engl. J. Med., **281**:1137, 1969.
33. Seldon, R., Lee, S., Wang, W. L., Bennet, J. V. and Eickoff, T. C.: Nosocomial Klebsiella infections: Intestinal Colonization as a Reservoir. Ann. Int. Med., **74**:657, 1971.
34. Mortimer, E. A., Lipsitz, P. J., Wolinsky, E., Gonzaga, A. J. and Rammelkamp, C. H.: Transmission of Staphylococci between Newborns. Am. J. Dis. Child., **104**:289, 1962.
35. Rammelkamp, C. H., Jr., Mortimer, E. A., Jr., and Wolinsky, E.: Transmission of Streptococcal and Staphylococcal Infections. Ann. Int. Med., **60**:753, 1964.
36. Miller, R. M., Polakavetz, S. H., Hornick, R. B. and Cowley, R. A.: Infections Acquired by the Severely Traumatized Patient. Surg. Gynecol. Obstet., **137**:7, 1973.
37. Schweinburg, F. B., Frank, H. A. and Fine, J.: Bacterial Factor in Experimental Hemorrhagic Shock. Am. J. Physiol., **179**:532, 1954.

Combined Surgical and Nutritional Management of Patients with Acute Mesenteric Vascular Occlusion

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IN 1936 DUNPHY POINTED OUT that a previous history of abdominal pain can be elicited from almost half the patients who present with acute mesenteric vascular occlusion.[4] However, the implied hope that intestinal ischemia might be treated electively in the preocclusive state has not been borne out. Surgeons continue to see massive midgut necrosis and are forced to resect extensive lengths of intestine in an attempt to salvage the life of a critically ill patient. Even when this is successful, the extent of resection necessitated by sudden occlusion of the superior mesenteric artery results in severe nutritional problems. The advent of vascular surgery has made possible a direct attack on impaired arterial blood flow but despite the fact that such techniques have now been available for 20 years they have failed to alter the poor overall survival rate of these patients. An embolus lodged in a normal mesenteric vascular tree requires only early recognition for effective surgical therapy and successful rehabilitation. Unfortunately, arterial thrombosis in an atherosclerotic superior mesenteric artery is a far more common event and restoration of normal mesenteric circulation is less likely to be successful. The combination of proximal revascularization and limited resection can be used in conjunction with the recent advances in surgical nutrition and may improve the outlook for these elderly atherosclerotic patients.

Material

Patients with mesenteric infarction must be classified in the light of the underlying etiology. While embolization, enteritis, and infarction without major vessel occlusion have been described, the present report deals only with acute arterial thrombosis super-imposed on chronic atherosclerotic disease. A review of the Presbyterian Hospital experience from 1950 to 1970 disclosed 30 patients in this category. Their pertinent clinical and pathological features are summarized in Table 1. Although gangrene involving the entire small bowel from just distal to the ligament of Treitz to the mid transverse colon would be expected on the basis of the blood supply of the superior mesenteric artery sudden occlusion of this vessel resulted in a variable pattern of ischemic change. Twenty-four of the 30 patients had vascular compromise in the expected superior mesenteric artery distribution but the actual bowel wall changes varied from frank gangrene to reversible ischemia. Careful review of the operative findings in these patients revealed that the bowel involved by full thickness gangrene was usually in the distal jejunum or ileum and the reversible changes most often involved the proximal jejunum or right colon.

Six of the total group of 30 patients with atherosclerotic thrombosis had lesser degrees of involvement with sufficient normal bowel to allow a limited, and nutritionally safe, resection. These patients could be properly managed without any need for revascularization. Clearly, patients who can be successfully treated with a limited resection constitute a fortunate few in the Presbyterian Hospital experience.

Resection of the involved bowel has been the traditional surgical approach to intestinal ischemia. Surgeons faced with the necessity for a massive resection are frequently comforted by numerous reports of survival

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following radical extirpations.[1,3,6,7,9] A review of these reports, however, reveals that the survivors are young and have a normal mesenteric arterial system. Elderly atherosclerotic patients evidently cannot survive the nutritional impact of resections that leave only a foot or two of jejunum anastomosed to the transverse colon. Unfortunately, this is the usual resection forced upon the surgeon in patients with superior mesenteric artery thrombosis if the anastomosis is to join only bowel that has a normal blood supply.

The prospect of lethal malnutrition following extensive resection of portions of the small and large intestine has led to the suggestion that the traditional surgical approach be modified. Shaw and Rutledge[10] advocated a second look operation that would allow the removal of only irreversibly damaged intestine at the time of the original exploration. This approach has been primarily associated with embolectomy where severely ischemic bowel may still survive following the restoration of a normal blood supply.

New approaches can also be adapted to atherosclerotic thrombosis even though restoration of normal blood supply is far less likely. In the three most recent patients who presented with atherosclerotic thrombosis we have combined a modified revascularization procedure with resection of irreversibly ischemic intestine in an effort to preserve adequate intestine for nutritional homeostasis. These three patients were not included in Table 1 and all had ischemic change involving the entire distribution of the superior mesenteric artery. Treatment consisted of a combination of revascularization and resection as outlined below.

TABLE I

PT	AGE	SEX	DISTRIBUTION	THERAPY	COURSE
1	77	M	1,2,3,4	resection	d
2	87	M	1,2,3,4	no resection	d
3	68	M	1,2,3,4	no resection	d
4	77	M	1,2,3,4	no resection	d
5	68	M	1,2,3,4	no resection	d
6	72	M	1,2,3,4	no resection	d
7	65	M	1,2,3,4	no resection	d
8	67	M	1,2,3,4	resection	d
9	82	F	1,2	no resection	d
10	65	M	1,2	no resection	d
11	80	F	1,2,3,4	no resection	d
12	80	F	1,2,3,4	resection	d
13	69	M	1,2,3,4	no resection	d
14	81	M	1,2,3,4	no resection	d
15	77	M	1,2,3,4	resection	d
16	45	F	1,2	resection	l
17	73	F	1,2,3,4	resection	l
18	54	F	1,2,3,4	no resection	d
19	50	F	1,2,3,4	resection	d
20	80	M	1,2,3,4	resection	l
21	51	F	1,2	thrombectomy	l
22	71	F	1,2	resection	l
23	63	F	1,2,3,4	no resection	d
24	67	F	1,2	resection	d
25	71	F	1,2,3,4	no resection	d
26	56	M	1,2,3,4	no resection	d
27	70	F	1,2,3,4	resection	d
28	61	M	1,2,3,4	no resection	d
29	55	M	1,2,3,4	no resection	d
30	47	M	1,2,3,4	resection	d

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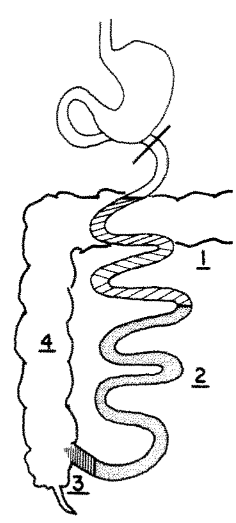

TABLE 1. Thirty patients with sudden proximal occlusion of the superior mesenteric artery seen between 1950 and 1970. The involved areas at the time of laparotomy have been divided into jejunum (1), ileum (2), ileocecal valve (3) and right colon (4). It is evident that most patients died (d) and only 5 survived (L).

Surgical Technique

Access to the origin of the superior mesenteric artery constitutes a major challenge. Exposure is hampered by the presence of the portal vein, neck of the pancreas with its abundant vascular tributaries and the thick lymphatic tissues in the root of the mesentery. On the other hand, the artery is readily accessible at the root of the small bowel mesentery as shown in Fig. 1. Exposure in this location can be accomplished rapidly and usually is only 3–4 cm. from the actual aortic origin. This has been the traditional site for performing an embolectomy.[15] The transverse colon can be retracted superiorly and an incision made on the right side of the root of the small intestinal mesentery. The firm pulseless superior mesenteric artery is readily identified. The artery must be traced distally in the mesentery and should be adequately exposed in order to identify the first 4 to 5 jejunal branches as well as the mid-colic (Fig. 2). When the artery is opened attention is first directed to the distal vascular bed. Back bleeding is usually sluggish or absent and the proximal artery remains occluded. A small Fogarty catheter is then inserted and passed as far down the superior mesenteric artery as possible in order to remove clotted blood. Reverse irrigation through a more distal arteriotomy has been described and may be helpful.[8] We formerly terminated the procedure at

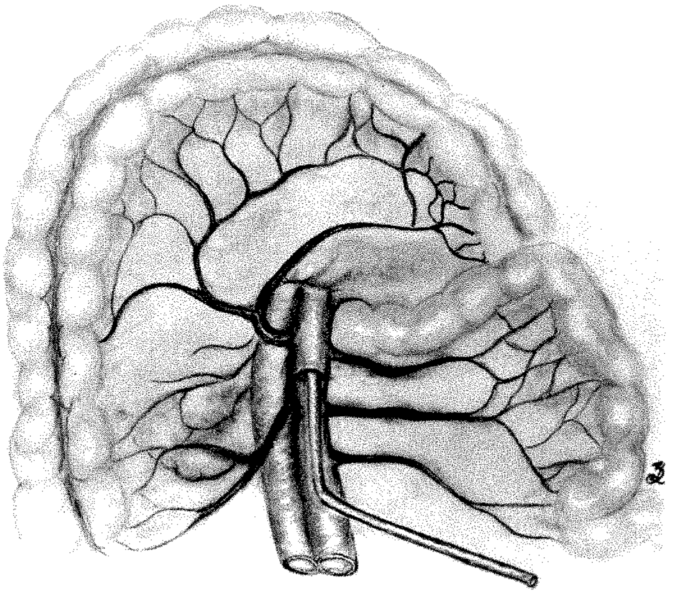

FIG. 1. Superior mesenteric artery and vein in the root of the small bowel mesentery.

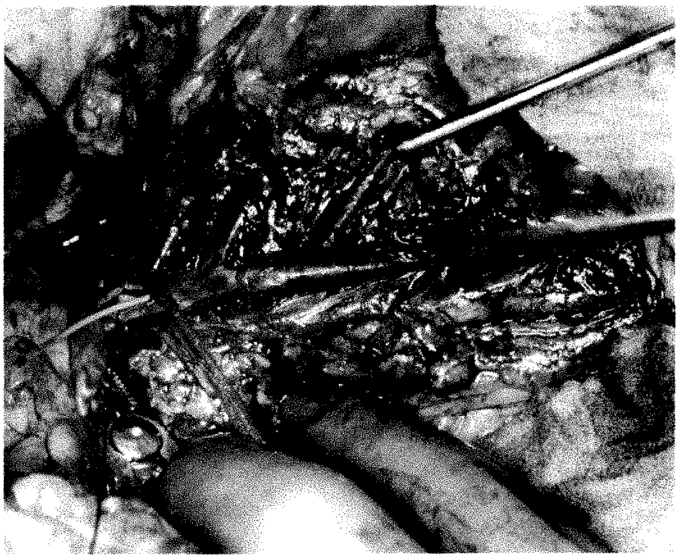

FIG. 2. Superior mesenteric artery and its proximal jejunal branches. The Fogarty catheter has been directed into the branch indicated by the sucker. The arteriotomy was made at the level of the first jejunal branch and the mid colic although neither vessel is well seen in this photograph.

that point and turned to the proximal portion of the artery. Pulsatile flow could usually be reestablished in the main vessel but the bowel failed to improve and the artery soon reoccluded. It appeared that the blood was not reaching the capillary bed in the intestinal wall and without run off rethrombosis of the artery was inevitable. When the proximal jejunal branches of the superior mesenteric artery are exposed it is possible to direct the Fogarty catheter into individual branches. These vessels are large enough so that the catheter can be passed to within less than 1 cm. of the intestinal wall. The mid colic artery can be dealt with in similar fashion and after the distal arterial tree is thus prepared a "blind" endarterectomy is performed on the proximal superior mesenteric artery through the same arteriotomy. We have not found it necessary to control the common iliac arteries in order to prevent dislodgement of plaque and clot into the legs but care is needed to avoid this complication. As a rule arterial pressure will force clot and atheromatous material back out through the arteriotomy. Finally the arteriotomy is closed in the usual fashion.

Discussion

The surgical approach to the catastrophe of acute mesenteric artery occlusion in the elderly atherosclerotic patient must not only consider immediate survival but also the preservation of a nutritionally adequate length of small bowel. Proximal revascularization of the superior mesenteric artery by the technique described above made it possible to preserve the proximal 3 feet of jejunum and the right colon in 2 of 3 patients in which it was attempted. In the one unsuccessful case extraction of clot from the mid colic failed to reestablish proper pulsatile flow in this vessel. There was no detectable improvement in the right colon which was not resected and the patient died 30 hours later. The exact status of the bowel at that time remains unknown since no postmortem examination was obtained but the clinical evidence suggested advancing intestinal gangrene.

It has not been necessary to remove clots from individual branches of the superior mesenteric artery when the proximal artery is occluded by an embolus. In the absence of generalized atherosclerotic change involving all three of the unpaired abdominal vessels collateral circulation is adequate to prevent clotting distal to the point of obstruction. The situation is obviously different in atherosclerotic thrombosis where minimal collateral circulation results in extensive clotting in the distal arterial tree. Under these conditions ischemia progresses rapidly to full thickness gangrene. Furthermore, efforts at direct revascularization solely directed to the major trunk of the artery are unlikely to succeed. Very little additional time is needed to expose the larger proximal branches of the superior mesenteric artery and extraction of clot from these vessels may make it possible to restore blood flow through the proximal artery in a situation where complete revascularization would be an impossible goal. On review of the Presbyterian Hospital series of patients with acute superior mesenteric artery occlusion due to atherosclerosis, it is evident that the changes in the jejunum were usually reversible at the time of exploration while frank gangrene, when present, was almost inevitably confined to the ileum. This area can be resected without significant nutritional consequences provided that restoration of flow through the superior mesenteric artery and its proximal branches succeeds in preserving a minimum of 3 feet of jejunum and the right colon.

The metabolic impact of jejunoileal resection is evident in the postoperative period and optimum nutritional management is required. Recently developed techniques utilize both the intravenous and the oral route and are of great importance during the interval needed for maximum adaptation. Adaptation is defined by an increase in absorptive capacity and structurally this is achieved by villus hypertrophy. In addition to hypertrophy, hyperplasia may also occur. Whether an increase in the number of mucosal cells is associated with an increased work capacity per cell remains unclear. Enzyme activity in the mucosal cells of the small bowel remnant has been studied; some investigators[2] have found no significant increase in enzyme activity while others have found increased concentrations of digestive enzyme and what seem to be related elaborations of sub-cellular organelles (microvilli, internal cell membranes).[12]

By increasing absorptive surface and absorptive work the small bowel, shortened by resection, undergoes adaptation. It is in this context that the postoperative nutritional management must be considered. The use of intravenous hyperalimentation in these patients can provide important nutritional support during the postoperative preadapted period. It is of interest that the adaptive changes occur, and may even be enhanced, even though the stimulous of an inadequate caloric intake has been eliminated by intravenous alimentation.[13] The intestine appears to hypertrophy in response to a reduction in its mass and this process evidently does not require the patient to be in a catabolic state.[14]

There seems to be neither adaptive nor nutritional advantage in early oral feedings and during the first weeks following operation intravenous therapy is generally indicated. The enhanced absorption that accompanies adaptation seems to become clinically apparent at about one month following resection and is usually reflected by a decrease in the volume of diarrhea. During the stage of improving absorption oral feedings may consist only of water or skimmed milk and hypotonic balanced salt solutions. The balance of the nutritional requirements can be met by intravenous supplementation. Any increase in tonicity and volume of the oral feedings should be determined by the patient's ability to tolerate the osmotic load as reflected by the volume of diarrheal stools. In most cases, oral intake should not be started until the diarrhea is less than 3 liters per day. As a rule adequate fluid and electrolyte balance can be achieved by oral intake alone within several weeks but it is far more difficult to achieve an adequate caloric intake. Some success has been reported with an oral elemental diet containing L-amino acids, glucose, vitamins, minerals and ethyllineolate.[11] There is evidence that large quantities of intraluminal glucose will aid in the absorption of water and this mechanism may play a role in reducing diarrhea in these patients.[5]

Summary and Conclusions

The Presbyterian Hospital experience with acute superior mesenteric artery thrombosis secondary to atherosclerosis has been reviewed and 24 of the 30 patients had ischemic changes involving the entire distribution of the superior mesenteric artery. Although mesenteric artery revascularization with preservation of the entire intestine is theoretically possible, this goal was never achieved. Standard vascular techniques have usually failed in the elderly atherosclerotic patients in large part because the lack of collateral circulation results in extensive clotting in the distal mesenteric branches. The 83% mortality noted in the present series is typical and reflects the difficulties presented by this surgical emergency.

In the three most recent patients presenting with acute thrombosis, the larger proximal branches of the superior mesenteric artery were exposed and clots could then be extracted by selective manipulation of a Fogarty catheter into these branches. This approach made it possible to preserve the proximal jejunum and right colon (via the mid colic) in two of the patients even though complete revascularization was not accomplished.

The techniques of intravenous and oral alimentation now available will maintain such patients during the initial period of adaptation and justify the efforts involved in preserving a few extra feet of jejunum as well as the right colon. Early experience with proximal revascularization plus a limited distal bowel resection suggests that the combined approach may be more effective than either technique used alone.

References

1. Althansen, T., Doig, R., Uycyama, K. and Weiden, S.: Digestion and Absorption after Massive Resection of the Small Intestine. Gastroenterology, **16**:126, 1950.
2. Bury, K.: Carbohydrate Digestion and Absorption after Massive Resection of the Small Intestine. Surg. Gynecol. Obstet. **135**:177, 1972.
3. Cheir, K.: Massive Resection of the Small Intestine. Surgery, **65**:931, 1969.
4. Dunphy, J. E.: Abdominal Pain of Vascular Origin. Am. J. Med. Sci., **192**:109, 1936.
5. Kendall, F. E. and Hawkins, W. A.: Oral Glucose in Reduction of Jejunostomy Effluent. Lancet, **2**:411, 1971.
6. Kinney, J. M., Goldwyn, R. M., Barr, J. S. and Moore, F. D.: Loss of the entire jejunum, ileum, and right colon. JAMA, **179**:529, 1962.
7. Leonard, A., Levine, A., Wittner, R., Buchwald, H. and Varco, R.: Massive Small Bowel Resections: Operative and Dietary Management. Arch. Surg., **95**:429, 1967.
8. Marston, A.: Acute Mesenteric Vascular Occlusions. *In* Vascular Disorders of The Intestine. S. J. Boley, S. S. Schwartz and L. F. Williams, Jr., editors. New York, Appleton-Century-Crofts, 514–515, 1971.
9. Meyer, H.: Sixteen Year Survival Following Extensive Resection of the Small and Large Intestine for Thrombosis of the Superior Mesenteric Artery. Surgery, **51**:755, 1962.
10. Shaw, R. S. and Rutledge, R. H.: Superior Mesenteric Artery Embolectomy in the Treatment of Massive Mesenteric Infarction. New Engl. J. Med., **257**:595, 1957.
11. Thompson, W., Stephens, R., Randall, H. and Bowen, J.: Use of the "Space Diet" in the Management of a Patient with Extreme Short Bowel Syndrome. Am. J. Surg., **117**:449, 1969.
12. Tilson, M. D. and Wright, H. K.: Ultrastructural Correlation of Enhanced Sodium Absorption Following Small Bowel Resections. Surg. Forum, **22**:366, 1971.
13. Wilmore, D. W., Dudrick, S. J., Daly, J. M. and Vars, H. M.: The Role of Nutrition in the Adaption of the Small Intestine after Massive Resection. Surg. Gynecol. Obstet., **132**: 673, 1971.
14. Wright, H. K. and Tilson, M. D.: The Short Gut Syndrome. Current Problems in Surgery, June 1971.
15. Zuidema, G. D.: Surgical Management of Superior Mesenteric Arterial Emboli. Arch. Surg., **82**:267, 1961.

Long-term Effects of the Artificial Heart

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SINCE 1957, efforts have been made to develop an implantable artificial heart.[1,5–9] It was not until March of 1971, however, that an artificial heart was able to maintain a calf's life longer than 100 hours. This change in survival time occurred after, following the advice of Bernhard and LaFarge,[2] we began to use intimas of the artificial heart that were made rough by the application of Dacron fibrils. Since then, nine calves implanted with artificial hearts in this laboratory have survived over 100 hours; the longest survival time was 388 hours (14 days and two hours). Although short-term problems such as high hemolysis have been overcome, new long-term problems have surfaced. Some old problems, once thought to be minor, have proved to be important. The purpose of this paper is to present the results and to recognize the problems, learned from the calf that survived 14 days, which, as far as we know, is the longest survival to date.

Method and Material

Our present artificial hearts have the blood-handling parts (shortly called heart) inside the chest. They are driven by compressed air and the driving system is outside the chest, connected with two 6-foot tubes with the heart itself.

Heart

An 8 cm diameter aluminum base Kwan-Gett diaphragm-type heart made of Dacron-mesh-reinforced Silastic was used in this experiment (Figs. 1 and 2). The inner surfaces or intimas were covered with Dacron cloth, not because we prefer it, but because we ran out of Dacron fibrils. Four Bjork-Shiley valves (size 27A) were attached to the artificial heart with Silastic dispersion coated metal rings, without the use of sewing skirts. For the aortic and pulmonary artery outflow tracts, conventional 25 mm Dacron woven grafts were used. To connect the artificial ventricles to the natural atria, cuffs made of silastic covered with Dacron cloth were used.

Driving System

The Salt Lake pneumatic driving system* (a modification of an earlier system[7]) was used, consisting of an electronic control system, a pressure regulator, pressure reservoirs, dp/dt valve, three-way solenoid valve, and an exhaust pipe which may or may not be connected to a large vacuum tank (Fig. 3). The electronic control system, operated manually, has two variables: heart rate and per cent systole, shown by digital numbers on the front panel. A fixed heart rate of 100 beats/min. and 35% systole was used. Driving pressures were 6 psi and 4 psi for the left ventricle (LV) and right ventricle (RV) respectively. Vacuum ranging from 5 to 10 mmHg was applied during diastole. This was used to obtain a higher rate of diastolic filling and hence a higher cardiac output at a given atrial pressure and a given rate. For each artificial heart this is determined in a mock circulation. Cardiac output was calculated from the

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* May be obtained from Vital Assists, Inc., 30 Kensington Avenue, Salt Lake City, Utah 84112.

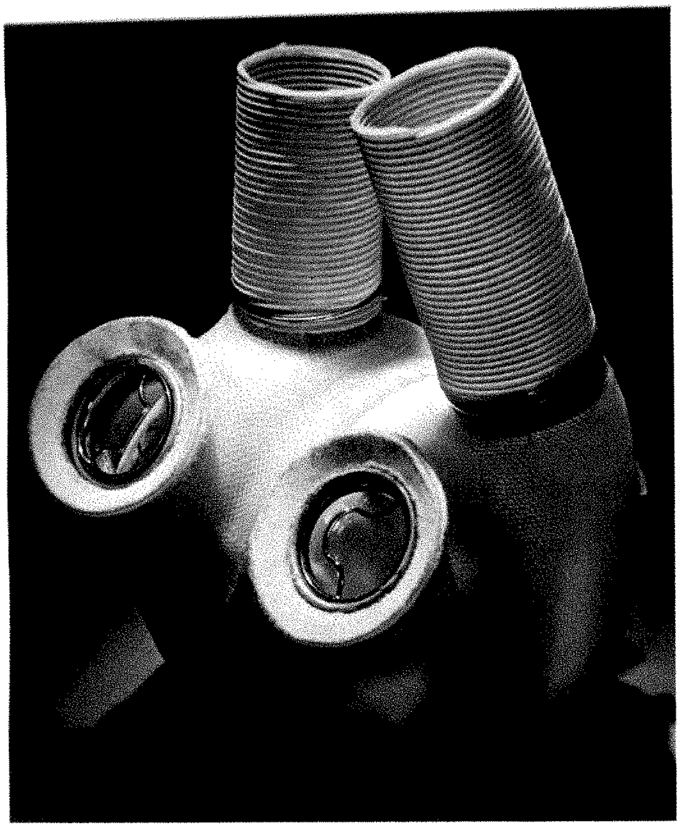

FIG. 1. Kwan-Gett hemispherical ventricles. The inlet valves can be seen. They are Bjork-Shiley valves. The flange around each inlet valve, the so-called atrial cuff, is used for sewing against the remnant of the natural atrium.

driving air line pressure curve (Fig. 4). Using the second derivative of the air line pressure curve, it was possible to determine the ejection time per beat (T), the cardiac output corresponding to any particular heart at various arterial pressures. This allowed continuous monitoring of cardiac output during the experiment.[3] A Starling's curve of the artificial heart relating atrial pressure to cardiac output was also made prior to implantation for each ventricle. As shown in Fig. 5, the K-G ventricle responds to Starling's Law of artificial hearts, which states that cardiac output increases with an increase in atrial filling pressure. With 10 mmHg of vacuum during diastole, and 6 psi of driving air pressure, at 0 mmHg of left atrial pressure cardiac output was 5 L/min, and at 20 mmHg the cardiac output was 11 L/min. This curve was made with a mean arterial pressure of 100 mmHg. Maximum slope of the curve was made with a mean arterial pressure of 100 mmHg. Maximum slope of the curve was approximately 0.4 L/min./mmHg of atrial pressure change.

Animal and Procedure

A 100 kg Holstein male calf was used. The calf was fasted, except for water, 24 hours prior to surgery and was given 2200 mg of Neomycin (10 mg/lb) the night before surgery to prevent gas formation inside the rumen during surgery.

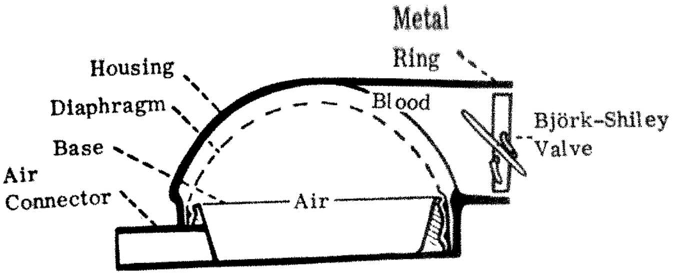

FIG. 2. Diagram of one side of the hemispherical ventricle at the end of systole. The diaphragm is displaced toward the outer housing to pump blood out into the aorta or pulmonary artery, which are not seen in this diagram. The construction is so that even in maximum systole, the diaphragm never touches the housing, so that red blood cells are not crushed.

The calf was anesthetized with 2 mg of scopolamine sulfate and 375 mg of sodium methoxital (Brevane) via an i.v. line and was intubated and restrained on the operating table in the supine position. Anesthesia was maintained by a Bird respirator with G.O.F. (50% N_2O, 50% O_2, 0.5 to 1.0% Fluothane).

The chest was opened by a midsternal splitting method. The superior vena cava (SVC) with azygos vein and the inferior vena cava (IVC) were dissected extrapericardially, and the pulmonary artery (PA) and aorta (Ao) were dissected intrapericardially. The hemiazygos vein, which drains into the coronary sinus, was ligated and cut. After the PA and Ao grafts were preclotted, 750 mg of heparin (5 mg/kg) was given via the i.v. line. The cannula for the heart-lung machine were inserted;

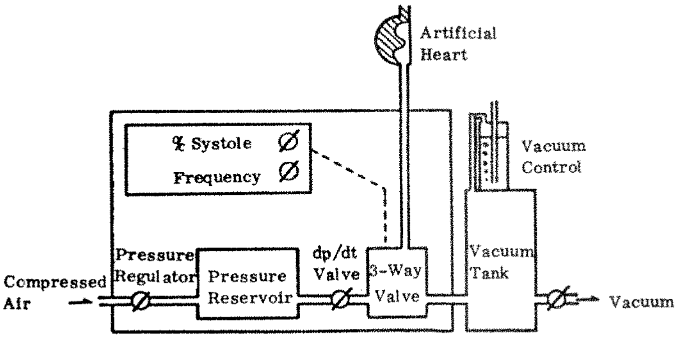

FIG. 3. Diagram of the driving system for one side. The artificial ventricle is driven pneumatically. The volume in the pressure reservoir was increased from 164 cc used in previous experiments, to 1600, resulting in an increase in dp/dt, therefore a dp/dt regulating valve is added. The three-way valve has a wide orifice to prevent obstruction of outflow or air during systole. To help diastolic filling, a large vacuum tank may be added. The vacuum is set by a valve but precisely controlled at five or at most, ten mm Hg by a tube in water as shown (vacuum control). Frequency and percent systole can be selected by digital number setting. (Driving system available from Vital Assists, Inc., 30 East Kensington Avenue, Salt Lake City, Utah 84115.)

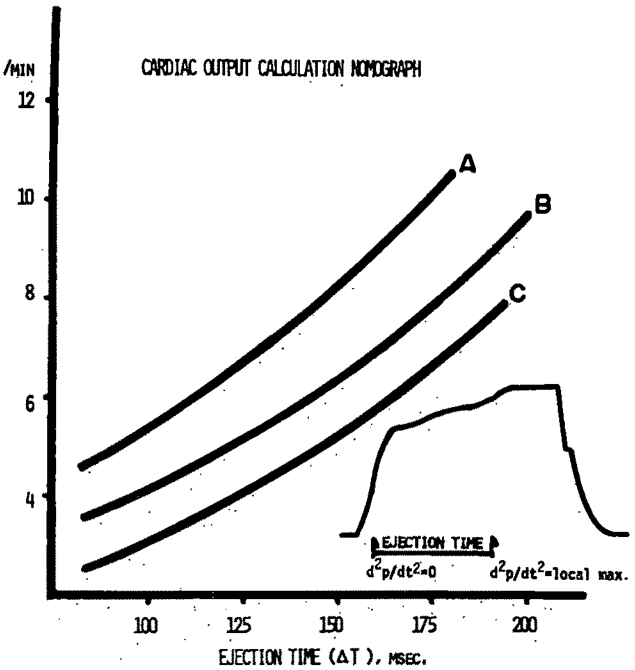

FIG. 4. Nomograph for calculation of cardiac output from ejection time (T) and mean arterial pressure. The insert in this figure shows the actual pressure change versus time. The ejection time was measured from the air line pressure curve using its second derivative d^2p/dt^2. With the K-G heart, it appears that blood ejection begins at the time of d^2p/dt^2 = local maximum point. These points are easily detected during the experiment when the second derivative (that is the acceleration) of the air pressure curve is used. T is 175 msec. and mean arterial pressure is 100 mm Hg, cardiac output will be 7.9 liters/min. "A" curve is with mean arterial pressure of 70 mm Hg; "B" curve with mean arterial pressure of 100 mm Hg, and "C" curve with mean arterial pressure of 130 mm Hg.

an IVC cannula via the right atrial appendage and an SVC cannula via the right external jugular vein. An arterial return cannula was put into the femoral artery. A Bentley's Temptrol oxygenator, primed with 2000 cc lactated Ringer's solution, 1000 cc of Rheomacrodex, 150 mg of heparin and 10 million units of penicillin, was used for cardiopulmonary bypass. After bypass was begun, the calf's natural ventricles and valves were carefully excised. The PA, ascending Ao, and both atria with valvular rings were left as remnants. Atrial cuffs were sutured to the right and left atria with continuous 3–0 silk sutures. The aortic and pulmonary arterial grafts were sutured to their natural counterparts with continuous 4–0 Tevedek atraumatic sutures. The left and right ventricles were flushed with carbon dioxide and were connected to the atrial cuffs. After the insertion of both ventricles was completed, they were primed with blood, and carbon dioxide inside the ventricles was removed by venting through ventricular taps. The same driving air tubes (⅜ inch inside diameter and 6 feet long) which were used on the mock circulation were connected to the ventricles, and pumping of the artificial heart was initiated. During cardiopulmonary bypass, normal temperature was maintained. Flow rate was 6.3 L/min. Bypass time was 85 minutes. Blood leakage was checked and repaired and the heparin was counteracted by slow infusion of 975 mg of protamine sulfate with 500 cc of normal saline. This is a one-to-one dose on the basis of the heparin inside the animal calculating transfused blood too. Fifty mEq of potassium chloride was administered at the same time. The chest was closed in the routine manner after placement of four drainage cannulas.

After surgery, the calf was placed in a metal cage which permitted it to stand and lie down as he wished. Throughout the experiment, periodic studies were made of arterial and venous pressures, cardiac output, pO_2, pCO_2, pH, base excess (M.E.), oxygen saturation, hematocrit, platelet count, clotting time, blood chemistry, blood volume, kidney function, and lung function.

Results

Postoperative Course

Soon after surgery, the calf became alert and triggered the Bird respirator. Arterial and venous pressures were low, indicating hypovolemia. After transfusion of 2000 cc of whole fresh cow blood (obtained from a slaughter house), arterial pressure increased to 170 mmHg systolic. At 6½ hours of artificial heart pumping, the endotracheal tube was removed and 4 L/min. of oxygen was supplied through a nasal oxygen tube. Nine and one-half hours after the heart had begun pumping, the calf stood by itself and remained standing 90 minutes without support. Cardiac output at this time was 6.2 to 7.8 L/min. At 22 hours of pumping, even with 4 L/min. of oxygen supply through a nasal tube, oxygen saturation decreased to 89% and pO_2 and pCO_2 were 69 and 57 respectively. Obviously there were lung problems. The calf was reintubated and put on the respirator with positive endexpiratory pressure (PEEP) up to 50 hours of pumping,

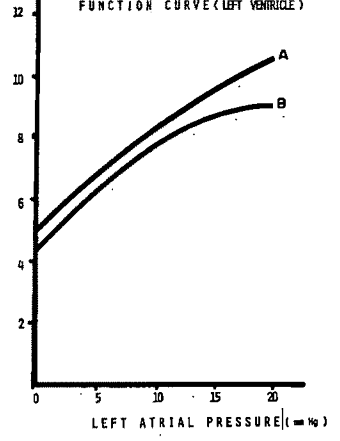

FIG. 5. Function curve of left ventricle. Cardiac output (C.O.) increases with an increase in atrial filling pressure (so-called Starling's Law of the Artificial Heart). The curve "A" is obtained with vacuums of 5 mm Hg and the curve "B" with no vacuum.

at which time the endotracheal tube was removed. From that time on the calf was given only nasal oxygen an average of less than 2 L/min. but sometimes up to 4 L/min., depending upon oxygen saturation. Oxygen saturation remained over 90% for most of the experiment. Although the calf was given whole blood until 13 hours of pumping to compensate for blood loss from chest drainage cannulas, and was given 1800 cc of whole blood at 184 hours, hematocrit decreased gradually, partly as a result of water retention evidenced by increased blood volume and partly on the basis of breakdown of red blood cells. Further blood transfusion was withheld because we did not want to disturb hematologic studies that were going on. The hematocrit fell to 15%; the calf deteriorated. After administration of an excess of I.V. fluid, pulmonary edema set in and the experiment was electively terminated at 338 hours.

Except during the last few hours, the general condition of the calf was good throughout the experiment; he ate, drank water, urinated, passed stool, and showed an interest in his surroundings.

Autopsy

Autopsy was performed immediately after termination of the experiment. The calf was suspended with a hoist by bone pins placed in the dorsal processes of the vertebrae. We always perform the autopsy in the normal standing position of the calf to evaluate the topographic conditions in the chest, and to see whether veins or atria are being compressed.

Findings at Autopsy

The heart fit well inside the chest cavity. There was no kinking of Ao, PA, SVC, or IVC, but there was an adhesion between the RA appendage and the chest wall, and the RA wall was pulled down toward the chest wall. This seems to have caused tension on the RA wall, resulting in some degree of inflow tract obstruction. There were no clots inside the RV, but there were clots on the rim of the LV. The atrial cuffs were narrowed by thrombus formation comprising one-third of the orifice area of the right cuff and half of the orifice area of the left cuff (Fig. 6).

The lungs were severely engorged and typical hepatization was seen. There was no evidence of embolization. The liver was found to be enlarged to almost twice its normal size. The gall bladder was distended with concentrated black bile. There were many small petechiae on the mucosa. The kidneys were enlarged and there was one large embolus in the right kidney. The corresponding area was infarcted but had no zonal hemorrhage. One liter of ascites was found in the abdominal cavity. The spleen was swollen and mushy upon sectioning. The blood vessels in the brain were a little distended

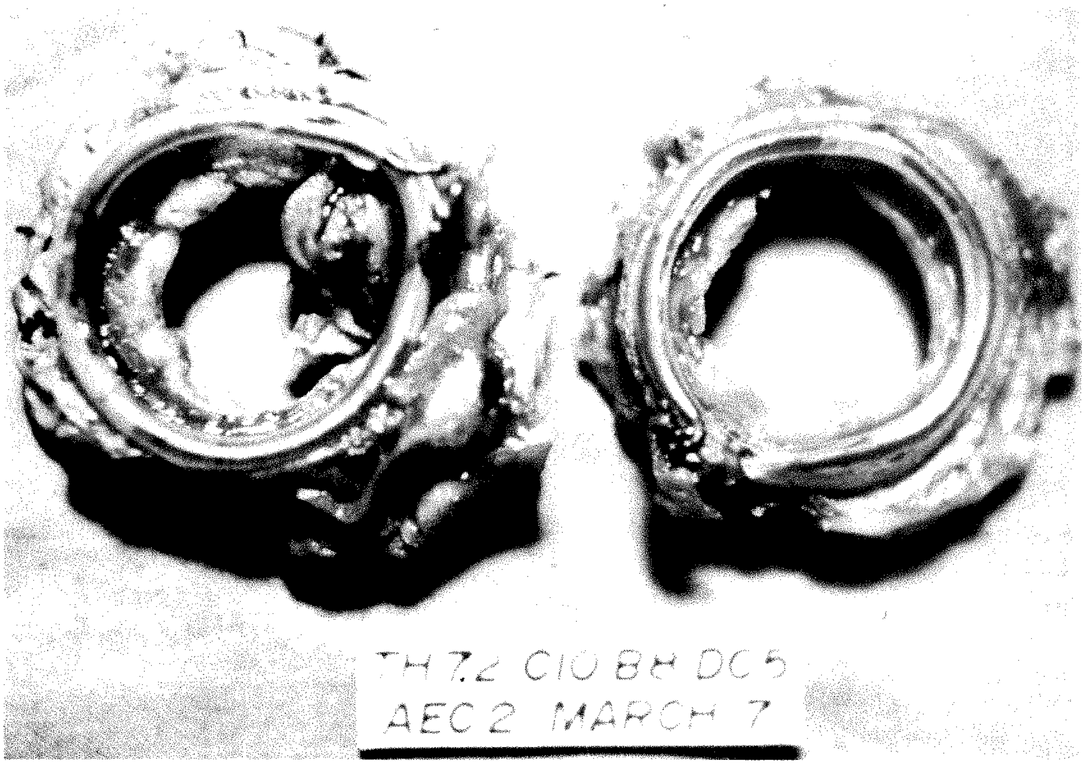

FIG. 6. Both left and right atrial cuffs were narrowed by thrombus formation inside. This may have been one reason for the gradual increase in venous pressure.

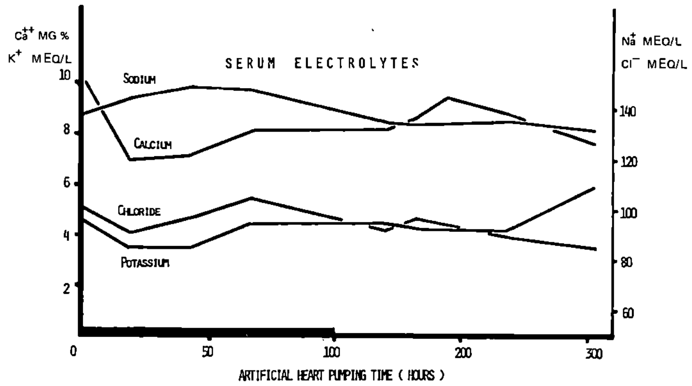

FIG. 7. Serum Electrolyte. Potassium decreased after surgery, as always after the use of a heart-lung machine. The calf was given 50 to 90 mEq as potassium chloride intravenously every day until the normal value was regained on the third postoperative day. The terminal rise in chloride was due to error in management. We have seen a tendency to low serum calcium in the animals, too. Except towards the end, these changes do not present a threat to the animal's life.

and filled with more blood than is usually seen at autopsy. There was no visible hemorrhage in the brain.

Some Results of Clinical Determination and Discussion of their Significance

Serum Electrolytes

Ca^{++} decreased from a control value of 10.3 mg per 100 ml to 7.0 mg after surgery, and although it gradually increased later, it never reached its original value (Fig. 7). Na^+ increased slightly after surgery until the third post-operative day, but decreased to less than control thereafter. K^+ and Cl^- levels could be maintained within a reasonable range except in the early post-operative stage. We should have given more K^+ intravenously after the cardiopulmonary bypass with the heart-lung machine.

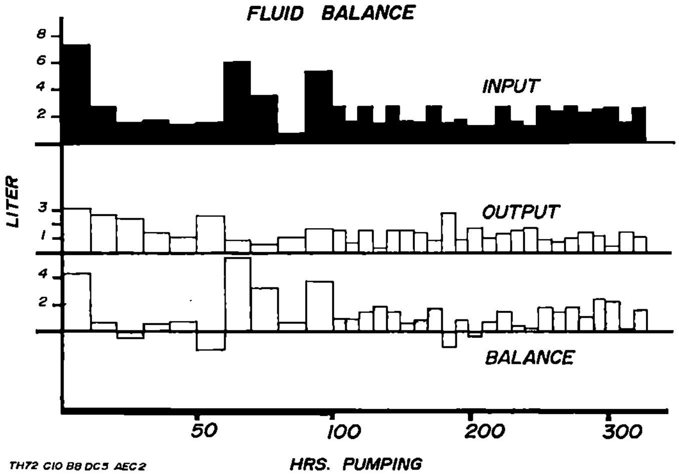

FIG. 8. Fluid balance of this animal shows a positive balance most of the time, confirming the animal's tendency to accumulate water. The balance is plotted in ten-hour periods, not in 24-hour periods.

There were no changes in electrolytes that at any time threatened the animal's survival.

SGOT, LDH

There was an initial increase in SGOT from 140 (control) to 2060 mm/ml on the second postoperative day, then a gradual decrease until it returned to a near-control value of 171 mm/ml on the tenth postoperative day; thereafter there was a tendency to increase. LDH fluctuated widely between a minimum of 577 mm/ml on the sixth postoperative day and a maximum of 1780 mm/ml on the fourth postoperative day. The SGOT probably reflects the consequences of surgery and heart-lung machine, and little else.

Kidney Function

Urine volume fluctuated between 325 cc and 2400 cc every 10 hours (Fig. 8). The average urine volume per 10-hour period was approximately 1000 ml during the first three hours of survival, but decreased to 640 after that time. BUN was 15 mg% before surgery and remained less than 20 mg% almost all of the pumping time, increasing to 25 mg% on the 13th postoperative day. Uric acid, which had a control value of 1.0 mg%, was always lower than 1.0 mg% except for 1.8 mg% on the 13th postoperative day. Serum creatinine (Fig. 9) was always less than the control value of three mg%. Throughout almost all of the pumping time, creatinine clearance remained between 80 ml and 100 ml, but decreased to 45 ml at the termination of the experiment. Obviously renal function was not impaired except as a terminal complication.

Coagulation Studies

The platelet count decreased initially to $216{,}000/mm^3$ at 19 hours of pumping, but recovered to $800{,}000/mm^3$ at 187 hours (Fig. 10). Clotting time fluctuated between 7 and 13 minutes, but was close to 8 minutes for most of the pumping time. Our coagulation specialist, Dr. E. J. Hershgold, calls this evidence of a compensated coagulopathy. The animal received no heparin. There is no clinical evidence that coagulation problems, except perhaps on the value rings, contributed importantly to the animal's death.

Blood Gas and Acid-Base Balances

pO_2, oxygen saturation showed somewhat lower values than what we expect at one mile above sea level in Salt Lake City (Figs. 11 and 12). The pCO_2 was also rather low. Throughout almost all of the artificial heart pumping time, pH's were over 7.4 and B.E. (base excess) was generally positive. We do not quite understand it but do not believe that this slight abnormality had any

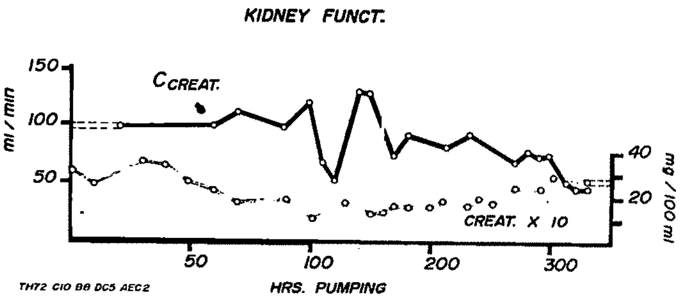

FIG. 9. Serum Creatinine and Creatinine Clearance. Serum creatinine concentration remained lower than control value during most of the pumping time. Creatinine clearance decreased somewhat after the sixth postoperative day but remained over 80% of its initial value until the tenth postoperative day. Renal failure is not a problem in our animals except as a terminal event.

grave consequences. However, there is evidence of diminished lung function.

Lung Function

Lung function was studied using a spirometer with a special mask for the calf (Figs. 13 and 14). Respiratory rate increased from a control value of 42/min. to 50/min. at 289 of pumping. Tidal volume decreased from a control value of 570 ml to 400 ml at 289 hours of pumping. Functional residual capacity (FRC) decreased markedly from 4555 ml to 2535 ml at 289 hours. Ventilation Equivalent of Oxygen (V.E.O_2), which had a control value of 5.4 liters air/100 ml O_2, decreased to 3.4 at 84 hours of pumping, recovered to 5.2 at 171 hours and decreased again to 3.9 at 289 hours. Oxygen consumption increased just after surgery and then remained almost constant at that level.

There is usually a gradual decrease in pulmonary function, although it was not serious in this animal, except in the terminal phase.

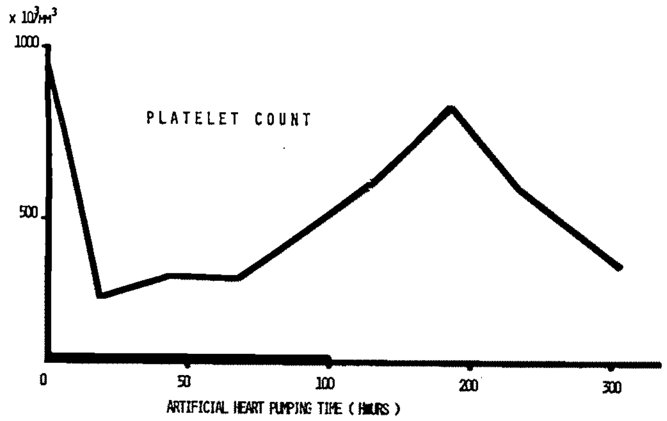

FIG. 10. Platelet Count. The normal platelet count for a calf is between 500,000 and 1,000,000. As always, there is a profound drop partly due to the use of a heart-lung machine, partly due to the effect of the artificial heart itself. After 60 hours, when the inside of the artificial heart is coated with a smooth layer of fibrin, the platelets regenerate.

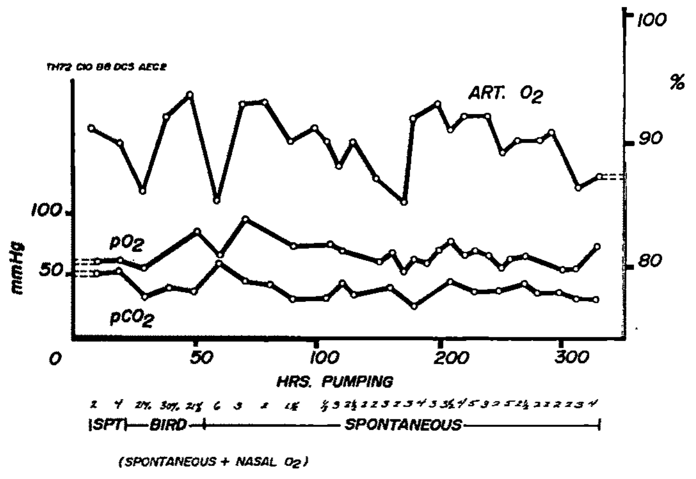

FIG. 11. Blood Gas. Blood gas studies were done by the Astrup micro method and showed somewhat low arterial oxygen saturation and low pO_2, even while supplemental oxygen was supplied through a nasal tube. The amounts in liters per minute are indicated. It should be remembered that our laboratory is one mile above sea level. Normal O_2 saturation in calves we find to be 92% and the pO_2 about 60. Oxygen lack was not a major problem in this calf.

Circulatory Functions

Arterial Pressure and Venous Pressure (Fig. 15). Arterial pressure was maintained at a reasonable level for most of the experiment, except initially and at the end of the experiment. The pulse pressure generated by the artificial heart was somewhat higher than that of the natural heart and was approximately one-half of systolic pressure. Venous pressure showed a gradual increase, which was not correlated with increase in arterial pressures.

Cardiac Output (Fig. 16). Cardiac output was rather constant and, contrary to our expectations, there was no correlation with venous pressure which became higher during the course of the experiment.

Blood Volume and Fluid Balance. As demonstrated in

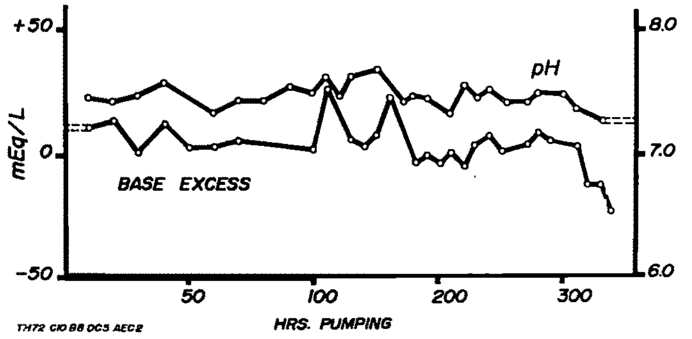

FIG. 12. Base Excess and pH. pH was slightly alkaline and Base Excess was positive throughout most of the pumping time. Important is that there was *no* metabolic acidosis.

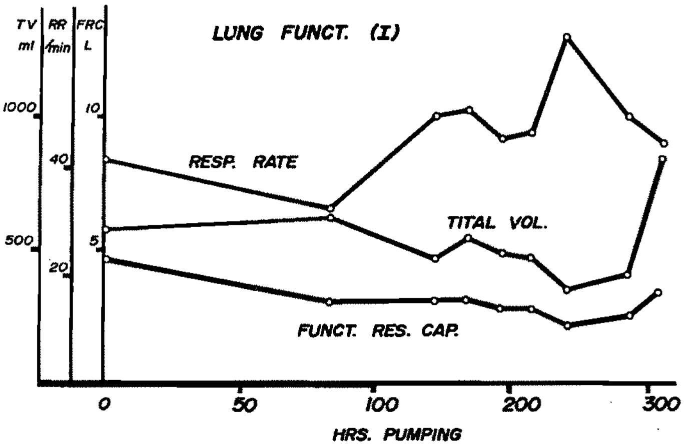

FIG. 13. Lung functions were studied with a spirometer. Respiratory rate (R.R.), tidal volume (T.V.), functional residual capacity (F.R.C.), remained reasonably good except toward the very end.

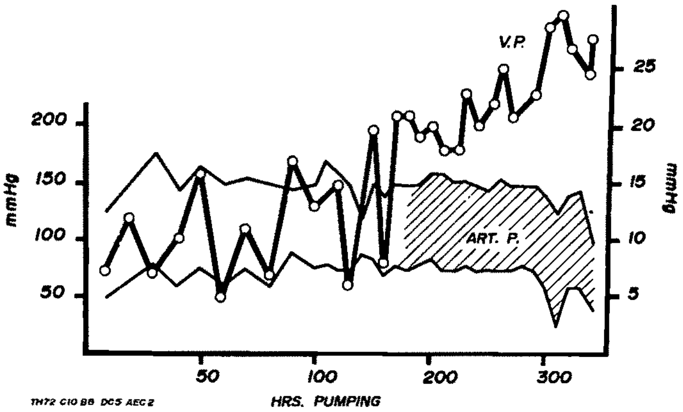

FIG. 15. The arterial pressure (scale at left) was within normal limits during most of the pumping time. Venous pressure increased gradually without correlation to arterial pressure, and finally reached 25 mm Hg (scale at right).

Fig. 17, there was an increase in blood volume, due to an increase in plasma volume. Cell volume seemed to have decreased very slightly. As was expected there was a slight positive fluid balance (Fig. 8).

We now recognize a serious problem. The venous pressure is too high from the very beginning. This may be due to the fact that the Starling's Curve for this particular Kwan-Gett heart was too far to the right and not steep enough. Therefore, a venous pressure of at least 10 mmHg was maintained by the animal to obtain the cardiac output of seven liters. The animal does this by increasing its blood volume. It behaves as a patient in right heart failure and reacts to Laxis with diuresis. Secondly, the venous pressure increases continuously without the desired result of increased cardiac output. Yet we know from studies in the mock circulation that to a venous pressure of 25 mmHg, this artificial heart would have reacted with an output of 11 liters/minute. Figure 18 shows the difference between the measured venous pressure and the effective venous pressure as it was estimated from the cardiac output. This suggests that there was some obstruction in the venous return. The cardiologist, Dr. A. C. Kralios, performed a catheterization for us on the last day of the experiment and proved that the pressures in the cranial and caudal venae cavae were identical. The obstruction was assumed to occur in the location of the natural right atrium. At autopsy, indeed a deformation of this part was found due to shrinking fibrinous adhesions of the right atrium to the chest wall. It formed a tent over the inflow opening. The tent wall could easily occlude in the inflow tract.

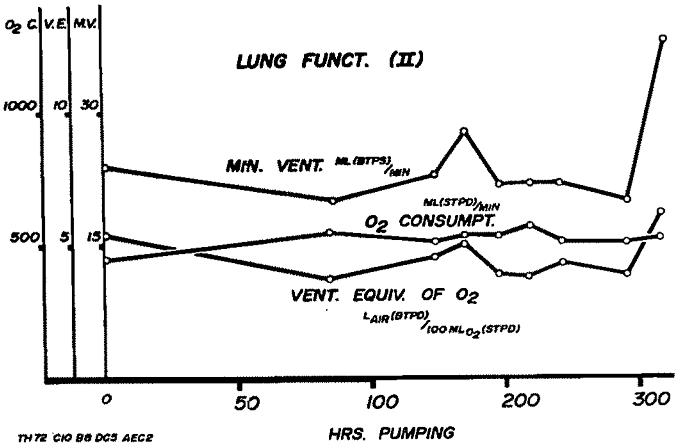

FIG. 14. Ventilation equivalent of oxygen (VEO_2) and minute volume (M.V.) showed a tendency to decline slightly throughout the experiment except toward the end when the animal was severely over-infused with saline. The graph illustrates deterioration of lung function, though it was very gradual. O_2 consumption increased slowly.

Hemolytic Icterus

Free Plasma Hemoglobin and Serum Bilirubin

Figure 19 demonstrates increases in both total and direct bilirubin. There is a difference between the two in

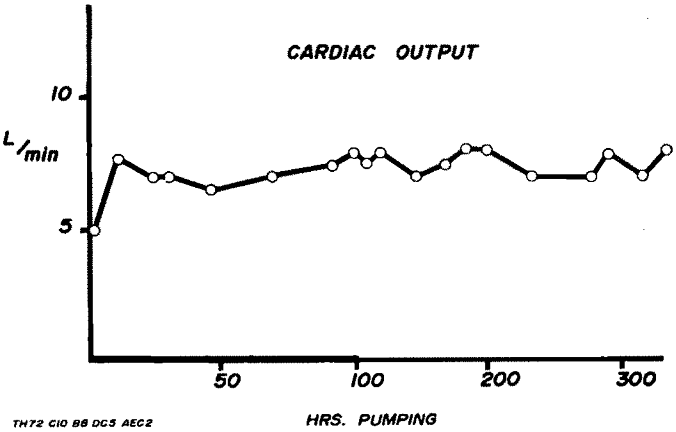

FIG. 16. The cardiac output was calculated from the nomograph shown in Fig. 4. For a calf with a body weight of 100 kg, 7 to 8 liters/min. of cardiac output is reasonable, but barely so.

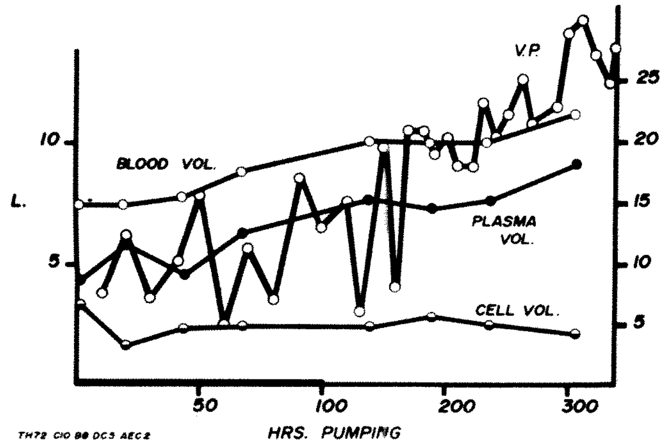

FIG. 17. Blood volume study showed an increase in blood volume which is due to increase in plasma volume since the cell volume did not increase, and towards the end, actually decreased. The increase in blood volume correlates with the increase in V.P. which is super-imposed in this figure.

terms of the onset and increase. Total bilirubin started to increase on the second postoperative day and direct bilirubin on the eighth postoperative day. Hemolysis was less than 5 mg% for most of the artificial heart pumping time.

Although the hemolysis was so slight that it could not be seen with the naked eye, it caused an increase in the indirect bilirubin. This in turn caused the bile to be dark and thick, obstructing some bile ducts as we will see later. This artificial heart was not coated with fibrils but with Dacron cloth. We have seen in other experiments that the degree of hemolysis is roughly proportional to the degree of roughness of the intima.

Histopathology

Microscopic examination of a section of the lung revealed numerous perivascular hemorrhages. A considerable number of alveoli contained fluid. These changes were probably terminal and partly induced by a large infusion of saline given shortly before termination. In the kidney, there was a large infarction resulting in necrosis and hemorrhage. This may well have originated either from the thrombus on the inflow valve of the left ventricle or from one of the many indwelling cannulas. In one section a small septic embolus had lodged in the glomerular tuft. No hemoglobin casts were found. The spleen was moderately congested with evidence of intravascular hemolysis, as characterized by the marked accumulation of hemosiderin in the reticuloendothelial cells of the spleen. There was an extreme accumulation of bile in the biliary canaliculi, indicating that severe biliary stasis was present in the liver. This was probably caused by the hemolysis which caused hemolytic icterus. There were also focal areas of necrosis, primarily in the area of the central veins where numerous hepatocytes showed coagulation-type necrosis. There were no significant abnormalities noted in the adrenals. In the brain there was marked evidence of perivascular edema present in all sections, but there was no hemorrhage or vascular thrombi.

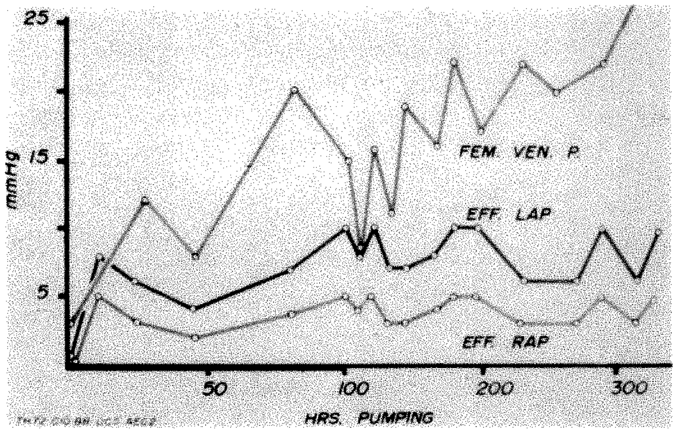

FIG. 18. Venous pressure is high although effective Left Atrial Pressure and Right Atrial Pressure are apparently low, indicating an obstruction between the venae cavae and the R.A.

Discussion

As we are able to maintain calves for increasing periods of time with implanted artificial hearts, better evaluation of the function of the artificial heart becomes possible. Although this experiment demonstrates the possibility of sustaining a calf's life for 14 days, the experiment showed us problems which have to be solved in the future. These include:

1. Disseminated Intravascular Coagulation[4]

The major problem recently was disseminated intravascular coagulation (D.I.C.) In our previous experi-

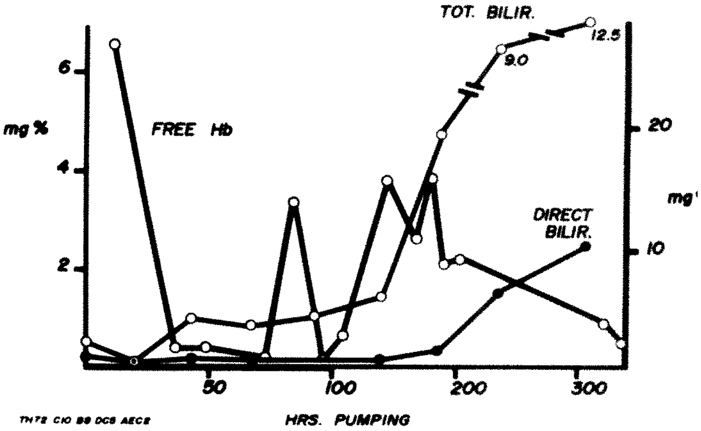

FIG. 19. Free Hemoglobin and Bilirubin. The scale for the free hemoglobin is on the right side of the graph. The value was initially elevated partly due to the heart-lung machine. Later the free hemoglobin levels became lower than 5 mg%. Slight elevations to 15 may have been due to blood transfusions. The total bilirubin increased earlier than the direct, indicating that the icterus was hemolytic in origin.

ments we could maintain the value for blood clotting factors within normal ranges, and in this particular experiment a recovery of platelet count with almost normal clotting time was seen. Normal values for clotting factors do not necessarily mean the absence of D.I.C. We know for example that although the number of platelets is normal, the adhesiveness of the platelets may be impaired. Our hematologist, Dr. Hershgold,[4] speaks of a compensated coagulopathy. In this particular experiment there is no evidence that D.I.C. carried much weight in the ultimate decline of the animal, although the possibility exists that it is at least partly responsible for changes in the pulmonary vasculature and function.

2. *Respiratory Distress Syndrome (R.D.S.)*

R.D.S. has been observed and described in many of our animals sustained with artificial hearts. Lung complications were mild in this case except toward the end. The calf was off the respirator most of the pumping time, but the experiment terminated primarily because of pulmonary edema. Almost all of our long survivals have shown pulmonary insufficiency in their postoperative course. In the fall of 1971 we began using a driving system with increased volume in the pressure reservoir (from 164 ml to 1600 ml) and higher driving pressure (4 psi) for the right side to increase cardiac output for any given right atrial pressure. We could improve the artificial heart's function curve, but it resulted in high peaked PA pressures and high dp/dt of the PA pressure. If and how much of a role they play in the generation of R.D.S. is not clear at this time. Low Ventilation Equivalent of O_2 seemed to indicate arteriovenous shunting with low oxygen diffusion through the alveolar-capillary membrane. Microscopically we have seen hyaline membranes and all the different pathological changes of the R.D.S. in the lungs of other animals. The lungs of this calf mainly showed acute changes which can be explained as terminal.

3. *Symptoms of Right Heart Failure*

High venous pressure, ascites increased blood volume, liver congestion, centrolobular hepatic necrosis, diuretic response to Lasix. The K-G heart is able to pump up to 11 L/min. of blood, thought to be enough cardiac output to maintain a calf's life. The studies in pH and base excess showed the tissue perfusion sufficied for adequate oxygen delivery or at least indicated that there was no metabolic acidosis, except at the very end. Compared with the natural healthy calf heart, however, it still has a much flatter Starling's curve. As described in the results, one mmHg increase in atrial pressure caused at most 0.4 L/min. of increase in cardiac output. The natural heart has a maximum slope which is almost ten times that of the artificial heart's. We need a heart which is more sensitive to the changes of input pressure and that gives a higher output at atrial pressures of 0 to 5 mmHg. In this animal and in many of our other animals sustained with artificial hearts, there has been an obstruction somewhere in the inflow towards the artificial ventricles. The space available for the artificial heart is small and kinking or obstruction of the vein, natural atria, or junction between them and the artificial heart occurs easily. Undue suction of the ventricles when transmitted to the soft material structures causes them to collapse. All of these factors lead to the clinical picture of right heart failure, or if you prefer, constrictive pericarditis.

4. *Hemolytic Icterus*

The Dacron cloth intima used in this experiment causes far more initial hemolysis than the Dacron fibrils intima that we have used before and after this experiment. In earlier experiments, when high hemolysis (over 50 mg%) occurred, the result was acute renal failure by hemoglobin cast. With improvements in the artificial heart, hemolysis has been much lower. However, it now appears that with longer survival times, even a low level of hemolysis, so low that it is not visible in the serum, may cause anemia and jaundice, resulting in liver damage. There might be brain damage if bilirubin concentration in the serum exceeds 20 mg% acutely. Chronically, even low bilirubin concentrations, 5 mg per 100 ml may cause liver damage. Our calf showed 4.8 mg% of serum bilirubin on the eighth postoperative day, and higher values thereafter.

5. *Infection*

Infection was not a serious problem in this particular case, as it has been sometimes in other artificial heart experiments. The presence of a big foreign object such as an artificial heart, driving lines, and pressure monitoring lines indwelling through the chest wall and dead space around the heart because of the difference in size and shape between the natural heart and the artificial heart, make the calves susceptible to infection. Calves in our experience are more resistant than sheep.

Summary

A calf survived 338 hours (two weeks and two hours) after removal of its natural heart and replacement with a mechanical heart implanted in the chest cavity. The problems becoming evident in longer survival are:

1. Disseminated intravascular coagulation. Since we have used rough surfaces which hold onto the fibrin that is formed inside the artificial hearts, the consumption coagulopathy is usually compensated and causes little problems.

2. Lung complications. The lung complications vary greatly in different animals and, in this case, caused little trouble for 12 days.

3. Symptoms of right heart failure as explained by a slow Starling's cruve when the artificial heart is tested in a mock circulation and by improper fit of the artificial heart inside the chest, leads to obstruction of venous inflow.

4. Hemolytic icterus leading to liver damage. This becomes evident after a week or more and occurs, although there may be no visible hemolysis.

Acknowledgment

The help of the following members of the staff and consultants is appreciated: Dr. Jeff Peters, Mr. Neil Eastwood, Dr. M. Ghavamian, Ms. Lowana Reese, Dr. E. Hershgold, and Dr. K. Van Kampen.

Addendum

At the time of acceptance of this article (July 1973), a new design of artificial heart called Jarvik type III has a smaller ventrodorsal diameter. It does not encroach upon the venous structures. Problem 3) symptoms of right heart failure have not occurred in six consecutive animals up to 16 days' survival. In one animal, Problem 4) hemolytic anemia, which was slight anyway, began to improve after 12 days of pumping.

References

1. Akutsu, T. and Kloff, W. J.: Permanent Substitute for Valves and Hearts. ASAIO, **4**:230, 1958.
2. Bernhard, W. F., LaFarge, C. G., Robinson, T., Yun, I., Shirahige, K. and Kitrilakir, S.: An Improved Pump Interface for Left Ventricular Bypass. Ann. Surg., **168**:750, 1968.
3. Donovan, F. M., Jr.: Thermodynamic Study of the Artificial Heart Using a Volume Sensing Mock Circulation. Abstract to Biomedical Engineering Soc., April, 1972.
4. Hershgold, E. J., Kwan-Gett, C. S., Kawai, J. and Rowley, K.: Hemostasis, Coagulation, and the Total Artificial Heart. ASAIO, **18**:181, 1972.
5. Kolff, W. J.: The Artificial Heart—Research, Development or Invention? Diseases of the Chest, **56**:314, 1969.
6. Kolff, W. J.: The Artificial Heart. Haifa (Israel), Harvey Papers, Technion, 1972.
7. Kwan-Gett, C. S., Wu, Y., Collan, R., Jacobsen, S. and Kolff, W. J.: Total Replacement Artificial Heart and Driving System with Inherent Regulation of Cardiac Output. ASAIO, **15**:245, 1969.
8. Kwan-Gett, C. S., Zwart, H. J., Kralios, A. C., Kessler, T., Backman, K. and Kolff, W. J.: A Prosthetic Heart with Hemispherical Ventricles Designed for Low Hemolytic Action. ASAIO, **16**:409, 1970.
9. Norton, S. H., Akutsu, T., and Kloff, W. J.: Artificial Heart with Antivacuum Balloons. ASAIO, **8**:131, 1962.

Further Studies of Endotoxin and Alveolocapillary Permeability:

Effect of Steroid Pre-Treatment and Complement Depletion

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HISTOLOGIC CHANGES IN THE LUNGS are seen following endotoxin administration in experimental animals.[4] Although leukocyte adherence to lung capillaries is the first detectable finding after endotoxin, leukocyte aggregation, endothelial bleb formation and degeneration of alveolar cells are also seen. Associated with these morphologic alterations is an accumulating body of evidence to suggest other functional changes also are occurring.[2,6,8,12] Recently, it was demonstrated in this laboratory that endotoxin causes an increase in the alveolocapillary permeability coefficient in the isolated perfused canine lung.[2] Increased precapillary and postcapillary resistances,[6,8] increased perivascular lung water[12] and decreased surfactant[4] have also been described.

The present authors studied the effect of corticosteroid pretreatment on the development of increased alveolocapillary permeability seen after endotoxin. In addition, we studied the influence of complement depletion on the ability of endotoxin to induce increased permeability.

Materials and Methods

The isolated perfused canine lung was used. This method has been described in detail[2,13] previously. Briefly, dogs were heparinized, anesthetized with Pentobarbital Sodium 30 mg/Kg and ventilated with 100% oxygen by endotracheal tube. After 30 minutes the trachea was clamped and the animals were exsanguinated. The collapsed and atelectatic left lower lobe was removed and connected to an isolated perfusion circuit utilizing autologous heparinized plasma. The vascular system was energized by a small pulsatile pump, at a constant flow rate of 140 ml per min. The lung was placed in a saline filled plethysmograph and the collapsed alveolar compartment then filled with Ringer's lactate solution containing 50 microcuries of ^{131}I labeled albumin which had been previously dialysed, to remove free ^{131}I. The appearance rate of labeled albumin in the vascular compartment was measured by scintillation detector* from 3 ml samples of plasma taken at 30 minute intervals for periods of 5 to 6 hours. All samples were returned to the vascular compartment after activity had been counted.

The plasma perfusate was gassed with room air, containing 5% CO_2. Perfusions were at room temperature. Pressures in the arterial side were monitored throughout by a Stathem strain gauge transducer connected to a Sanborn Recorder. After an initial perfusion period of 3 hours, purified *E. coli* endotoxin† was added in doses of either 2 or 10 mgm/Kg. The dose was based on weight of lung tissue plus plasma.

Twenty-six dogs were divided into 5 experimental groups. Group I, (4 control lobes) underwent 3 hours of perfusion after which purified *E. coli* endotoxin was added to the vascular perfusate. Perfusion was continued for an additional 3 hours. In group II, (10 lobes) Hydrocortisone acetate in doses which ranged from 6 to 150 mgm/Kg was added to the perfusate shortly after

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* 2804 Scintillation Detector, Picker Nuclear Instruments, White Plains, N.Y.

† Difco Laboratories, Detroit, Michigan.

commencing the perfusion. Endotoxin was added to the perfusate after 3 hours. In Group III, (3 lobes) Methylprednisolone succinate 30 mg/Kg was placed in the perfusate shortly after perfusion commenced. After 3 hours endotoxin was added. In group IV, (3 lobes) autologous plasma was initially heated to 56°C for 30 minutes. This is a method which destroys complement factors C1, C2, C3, C4.[7] The plasma was then cooled and used to perfuse the lung. Endotoxin was added to the decomplemented perfusate. In Group V, (6 lobes) the plasma was heated for 15 minutes to 56°C. This destroys the heat labile complement factors C1 and C2, but does not affect the more heat stable complement factors C3 and C4.[7] After 3 hours of this perfusion endotoxin was then given. Samples of perfusate in groups IV and V were later analyzed *in vitro* for residual complement using the standard hemolytic assay of sensitized sheep red blood cells. Samples of lung tissue were taken at the end of the experiment and examined histologically after hematoxylin and eosin stain.

TABLE 2. *Lung Perfusion with Plasma. Hydrocortisone Acetate in Varying Dosages Given at Start of Perfusion. Endotoxin 2 mgm/Kg added after 3 hours. Permeability Calculated Before and After Endotoxin*

	Hydrocortisone mg/Kg	Permeability $\times 10^{-9}$ cm/sec		Mean Arterial Pressure mm/Hg.	
Dog#	Low Dosages	Control	Toxin	Control	Toxin
5	7	.145	.212	12	12
6	6	.996	2.019	15	15
7	6	.415	.396	13	13
8	30	1.12	17.56	24	24
9	30	3.90	8.78	20	20
10	30	3.64	11.00	13.4	13.0
Avg.		1.70	6.66	16.2	16.2
	High Dosage				
11	150	.623	.502	12.5	14.5
12	150	1.63	1.73	12.5	12.5
13	150	.928	.856	25	25
14	150*	.202	.190	15	15
Avg.		.846	.820	16.2	16.7

* Hydrocortisone given 30 min. after endotoxin.

Calculation of Permeability Change

The calculations and assumptions of this perfusion system have been previously described.[2,13] The formula for permeability (P) in cm/sec involves computing alveolar volume (Va) and vascular volume (Vb). The half time ($T_{1/2}$) to reach equilibrium concentration of isotope in alveolar and vascular compartments is obtained from appearance rate of isotope (counts per minute) in the plasma. The Log of differences between the calculated counts per minute at equilibrium versus observed counts per minute in the plasma yield a straight slope when plotted over time. Surface area (A) was obtained after the method of Taylor *et al.*,[13] by multiplying the lung weight (gm) by 661.

$$P = .693\, Va\, Vb/T_{1/2}\, A\, (Va + Vb)$$

Since each dog serves as his own control, comparison can be made on the effects of various agents on the appearance rate of isotope. From this the relative change in appearance rate and half times can be calculated and the corresponding permeability changes ascertained.

Results

In Group I, (4 controls) an increase in permeability of 91% was noted. The results in this small group are compared to a prior study of 5 canine lungs in which a permeability increase of 153% was noted.[2] The results in the 2 groups are reasonably consistent, when considering the small number of dogs in either group. In Group II, 10 lobes were pre-treated with varying doses of Hydrocortisone acetate, before administration of endotoxin. In the first 6 perfusions, low doses of steroid were given. Three lobes received 6–7 mgm/Kg and 3 others received 30 mgm/Kg. The permeability before endotoxin averaged 1.70×10^{-9} cm/sec and this increased to 6.66×10^{-9} cm/sec ($p < .01$). However, in 4 lobes given 150 mgm/Kg of steroid the permeability underwent no significant change after endotoxin administration. In fact there was slight, but insignificant decrease in permeability. There were no changes in the mean arterial perfusion

TABLE 1. *Lung Perfusion with Autologous Heparinized Plasma Under Oxygenated Conditions. Endotoxin 10 mgm/Kg Added after 3 Hours. Permeability Calculated Before and After Endotoxin*

	Permeability $\times 10^{-9}$ cm/sec		Mean Arterial Pressure mm/Hg	
Dog#	Control	Toxin	Control	Toxin
1	.242	.419	12	—
2	.168	.326	16	15
3	.080	.179	10	10
4	.133	.266	7	6
Avg.	.156	.298	8.75	10.3

TABLE 3. *Lung Perfusion with Plasma. High Doses of Methylprednisolone succinate given at start of Perfusion. Endotoxin 2 mgm/Kg Added after 3 hours*

		Permeability $\times 10^{-9}$ cm/sec		Perfusion Pressures	
Dog#	Methylprednisolone Mg/Kg	Control	Toxin	Control	Toxin
15	30	.854	.891	40	16.5
16	30	5.12	6.419	20	20
17	30*	.333	.527	24	25
Avg.		2.102	2.612	38	20.5

* Methylprednisolone given 30 min. after endotoxin.

TABLE 4. *Lung Perfusion with Plasma Previously Heated to 56° for 30 Min. Endotoxin 10 mgm/Kg Added after 3 Hours*

	Permeability $\times 10^{-9}$ cm/sec		Perfusion Pressure mmHg.	
Dog#	Control	Toxin	Control	Toxin
18	.104	.117	7	7
19	1.106	.824	10	10
20	.563	.625	10	10
Avg.	.591	.522	9	9

pressures. In dog No. 14 given Hydrocortisone 30 minutes after endotoxin there was no increase in permeability either.

In Group III, Methylprednisolone succinate 30 mgm/Kg was given. A 24.3% increase in permeability was noted following endotoxin administration. This is a small, but significant increase. In dog No. 17 the Methylprednisolone was given 30 minutes after endotoxin administration. There was also a significant increase in the permeability. In Group IV, 3 lobes were perfused with plasma which had been heated to 56° for 30 minutes, in order to destroy all complement factors. In this group there was a slight reduction in average permeability, although 2 of the 3 lobes had a slight increase in permeability. Changes were insignificant. In Group V, there was perfusion of the lungs with plasma which had undergone a brief period of heating to 56°C for 15 minutes to decomplement plasma partially by removing factors C1 and C2. In this group, 5 of 6 lobes demonstrated a decrease in permeability. In one instance, (dog No. 24) there was an increase in permeability, the reason for which is not apparent. Perfusion pressure changes in the last 2 groups did not show significant changes after endotoxin administration.

Studies of complement activity in plasma after the perfusion showed that hemolytic activity had been reduced to undetectable levels in Groups IV and V. This denotes absence of one or all complement components.

Histological examination of lungs after perfusion failed to reveal any obvious damage to capillary or alveolar walls in any of the groups.

TABLE 5. *Lung Perfusion with Plasma Previously Heated to 56° for 15 Min. Endotoxin 10 mgm/Kg Added after 3 hours*

	Permeability $\times 10^{-9}$ cm/sec		Perfusion Pressure mmHg.	
Dog#	Control	Toxin	Control	Toxin
21	1.61	0.62	11	11
22	0.97	0.51	35	38
23	0.779	0.484	18	—
24	0.142	0.205	17	—
25	2.131	.993	5	—
26	1.02	0.78	5	6
Avg.	1.11	.599	15	18.3

Discussion

These studies again show that endotoxin is associated with increased alveolocapillary permeability. Although pretreatment with low doses of Hydrocortisone acetate (up to 30 mgm/Kg) did not prevent increased permeability following endotoxin, pretreatment with massive doses of Hydrocortisone (150 mgm/Kg) protected the alveolocapillary membranes and no increased permeability occurred.

Pretreatment with the more potent steroid Methylprednisolone, also largely protect the alveolocapillary membrane; a small increase of 24% permeability after endotoxin was apparent. This increase was not as marked as in Group I (91% increase). Some unpublished observations in the laboratory have also indicated that Methylprednisolone when given to normal isolated perfused canine lobes causes a vasodilation. This is consistent with the studies of others[8,10] who noted reduction of systemic resistance after massive doses of steroids.

Endotoxin was used in doses known by previous study[2] to be sufficient to cause increased permeability (either 2 to 10 mgm/Kg). The different doses were arbitrarily chosen, so these experiments do not establish the threshold for endotoxin effect, nor do they permit comparisons between effectiveness of steroid versus decomplementation of plasma. But the data does indicate that endotoxin effect on permeability can be prevented by steroid administration or by complement depletion.

Mechanisms of Protection

Increased survival in experimental endotoxin shock and clinical gram negative septic shock have been described with treatment programs utilizing massive doses of cortico-steroids.[8,14] The exact mechanism of steroid action is not clear. Capillary membrane protection in the forelimb[8] and the small intestine has been demonstrated, as has lysosomal membrane stabilization.[5,15] Decreases in the pulmonary precapillary and post-capillary resistances,[8] found elevated after endotoxin administration, have also been noted.

There is up to 62% incidence of sepsis in patients with acute respiratory distress syndrome.[1] It is possible that such respiratory failure is in part due to increased alveolocapillary permeability. A combination of the above mentioned effects as well as others not yet described may account for the salutary effects of cortico steroids.

The role of complement in endotoxin induced damage is well established.[3,9,11] In the presence of complement, endotoxin proceeds to lyse cell walls and complement is depleted.[3,9] Schumer[11] has shown that when endotoxin is added to serum and sensitized sheep erythrocytes in the presence of cortico steroids, the endotoxin-induced hemolysis is decreased, either by decreasing complement or inhibiting complement fixation. This may explain part of the anti-complimentary effect of cortico steroids. From our study it appears possible that depletion of only the first 2 factors of the complement system may be sufficient to prevent the increased alveolocapillary permeability brought about by endotoxin. Further studies of the complement system are needed to resolve this point and are in progress.

Summary

1) The effects of cortico steroid pretreatment and complement depletion on endotoxin-induced increased alveolocapillary permeability were studied.

2) Pretreatment with small doses of cortico steroids had no effect in halting the increase in alveolocapillary permeability. Pretreatment with massive doses of Hydrocortisone abolished the increased permeability. Massive doses of Methylprednisolone blunted, but did not entirely prevent permeability increase.

3) Depletion of the first 2 complement factors, as well as depletion of all complement factors, prevents endotoxin-induced increased alveolocapillary permeability.

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References

1. Ashbaugh, E. and Petty, T. L.: Sepsis Complicating the Respiratory Distress Syndrome. Surg. Gynecol. Obstet., 135:865, 1972.
2. Cintora, I., Goodale, R. L. Jr. and Yamoor, A.: The Effect of Endotoxin on the Alveolocapillary Permeability Coefficient in Dog. J. Surg. Res., 13:59, 1972.
3. Day, N. K., Good, R. A., Finstad, J., Johannsen, R., Pickering, R. J. and Gewurz, H.: Interactions Between Endotoxic Lipopolysaccharides and the Complement System i the Sera of Lower Vertebrates. Proc. Soc. Exp. Biol. Med **133**:1397, 1970.
4. Harrison, L. H., Beller, J. J., Hinshaw, L. B., Coalson, J. and Greenfield, L. J.: Effects of Endotoxin on Pulmona Capillary Permeability Ultra Structure and Surfactan Surg. Gynecol. Obstet., **129**:723, 1969.
5. Janoff, A., Weissmann, G., Zweifach, B. W. and Thomas, L Pathogenesis of Experimental Shock IV. Studies of L sosomes in Normal and Tolerant Animals Subjected Lethal Trauma and Endotoxema. J. Exp. Med., **116**:45 1962.
6. Kuida, H., Hinshaw, L. B., Gilbert, R. P. and Visscher, M. B Effect of Gram Negative Endotoxin on Pulmonary Circ lation. Am. J. Physiol., **192**:335, 1958.
7. Kabat, E. A. and Mayer, M. M.: Complement and Compl ment Fixation. In Experimental Immuno Chemistry, 2n ed. Springfield (Ill.): Ch. C. Thomas, 133, 1961.
8. Motsay, G. J., Dietzman, R. H., Shultz, L. S., Romero, L. and Lillehei, R. C.: Effects of Massive Doses of Corti Steroids in Experimental and Clinical Gram-Negati Septic Shock. *In* Shock in Low and High Flow States. A sterdam, Excerpta Medica, 293, 1972.
9. Pillemer, L., Schoenberg, M. D., Blum, L. and Wurz, L Properdin System and Immunity II Interatcion of Properd System with Polysaccharides. Science, **122**:545, 1955.
10. Sambhi, M. P., Weil, M. H. and Udhoji, V. N.: Acute Pharm codynamic Effects of Glucocorticoids. Circulation, **31**:52 1963.
11. Schumer, W., Erve, P. R. and Obernolte, R. P.: Mechanis of Protection in Septic Shock. Surgery, **72**:119, 1972.
12. Snell, J. D. and Ramsey, L. H.: Pulmonary Edema as a R sult of Endotoxemia. Am. J. Physiol., **217**:170, 1969.
13. Taylor, A. E., Guyton, C. and Bishop, V. S.: Permeabili of the Alveolar Membrane to Solutes. Circ. Res., **16**:35 1965.
14. Weil, M. H. and Miller, B. S.: Experimental Studies Therapy of Circulatory Failure Produced by Endotoxi J. Lab. Clin. Med., **57**:683, 1961.
15. Weismann, G. and Thomas, L.: Studies on Lysosomes. Effects of Endotoxin, Endotoxin Tolerance and Cortiso on the Release of Acid Hydrolases From Granular Fracti of Rabbit Liver. J. Exp. Med., **116**:433, 1962.

Intestinal Control of Gastric Acid Secretion in the Rat

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A PREVIOUS REPORT FROM OUR LABORATORY[8] confirmed the fact that resection of the jejunum in rats resulted in an elevation of gastric acid secretion as collected from a Heidenhain pouch. We also found that intraperitoneal injection of a saline homogenate of jejunal mucosa caused a return of the gastric acidity to prejujunectomy levels. Thus we concluded that jejunal mucosa may contain an inhibitory factor to gastric acid production.

The question arose as to whether such an inhibitor could be found elsewhere in the small intestine. It has also been suggested that pyrogenic activity might have accounted for the depressant effect of the jejunal homogenate on gastric acid production. The present study was made to observe the effect of ileal mucosal homogenates on gastric acid production in jejunectomized rats. This was done to determine if ileal mucosa contains an inhibitory factor to gastric acid production or whether pyrogens might, indeed, be responsible.

Method

Using the method of Thorbjarnarson and colleagues,[12] with slight modification, denervated gastric pouches were created in 23 male white Wistar strain rats, weighing 300–500 grams. After an overnight fast, each was anesthetized with intraperitoneally administered pentobarbital. The abdomen was entered through a midline incision and the pouch cannula brought out through a right paramedian stab wound.

Post-operatively, the rats were fasted for 24 hours, given fluids only for 24 hours, and then given a standard solid diet. After several days of stabilization they were placed in restraining cages and gastric secretions were collected for a period of 3 hours. The rats were fasted overnight before each collection.

Titration was performed with 0.1 mls. of the collected gastric secretion against 0.1 N sodium hydroxide to an end point of pH 7. Each reading was repeated at least 3 times and the average taken and calculated in milleqivalents per hour. Once the control values were established, after 3 weeks, each rat was subjected to a jejunal resection from a point just distal to the ligament of Treitz to a point 38–40 cms. distally. Intestinal continuity was re-established by a single layer end-to-end anastomosis, using No. 5-0 silk sutures. After a period of stabilization, gastric secretions were again collected and measured as before.

Each rat was then given intraperitoneal injections of a jejunal mucosal homogenate prepared by homogenating the jejunal mucosa, scraped from the resected jejunum of another animal, with normal saline solution in the ratio of 1 ml. of intestinal mucosa to 3 mls. of normal saline solution. A 2.5 ml. aliquot of this fluid was used for each injection. Pouch secretions were then collected for the following three hours and measured as previously.

Ileal mucosal homogenates were then prepared as above and injected intraperitoneally into each rat. Again the pouch secretions were collected for 3 hours and measured as before. This procedure was repeated with jejunal mucosal homogenates cooled to −4°C. All collections in each rat were repeated on at least three occasions.

Results

Gastric acid secretion, as collected from a Heidenhain pouch in rats, is almost tripled after jejunectomy (Table 1). This change is highly significant ($p < 0.001$). The effect of injecting a jejunal mucosal homogenate into a jejunectomized rat is to revert the gastric acid secretion to control levels (Table 2). The actual measured differ-

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TABLE 1. *Gastric Acid Production (mEq/hr)*

Control Rats	Jejunectomized Rats
1.3 ± 0.7	3.8 ± 2.3

ence from the control level is insignificant ($p > 0.1$). The effect of injecting an ileal mucosal homogenate into a jejunectomized rat is to cause only an insignificant decrease from the high levels of acid secretion caused by the jejunectomy (Table 3) ($p < 0.1$). Injection of a cooled jejunal mucosal homogenate into a jejunectomized rat causes a decrease in the gastric acid secretion to control levels (Table 4). The difference between the effect of the cooled jejunal mucosal homogenate and that at room temperature is insignificant ($p < 0.2$).

Discussion

Other authors[2,5,10,11,13] have previously noted a greater increase in gastric acid secretion after resection of the proximal part of the small intestine than after a distal resection of the same length. This would suggest that any inhibiting factor to gastric acid secretion should be in the jejunum. Others[1,4,6,7] have observed an increase in gastric acid secretion after distal small intestinal resections. But they found this to occur after resection of very long segments of bowel, which may have included some jejunum. Fischer *et al.*[3] resected 75% of the small intestine in rats to produce increased gastric acid production. Rudick *et al*[9] demonstrated suppressors of gastric acid secretions in jejunal and ileal secretions of dogs and rats. This might be due to the action of pyrogens. Our results show that jejunal mucosal homogenate injections result in a decrease in gastric acid secretions in jejunectomized rats but ileal mucosal homogenate injections do not. This would suggest that an inhibitor to gastric acid secretions is found in jejunal mucosa but not in ileal mucosa. It would also tend to suggest that pyrogens, which should be no different in either homogenate, do not play a part.

Summary

Jejunectomy causes an increase in gastric acid secretion in rats. Jejunal mucosal homogenate causes this increased gastric acid secretion to decrease to control levels. Ileal mucosal homogenate does not cause gastric acid secretion to decrease to control levels. Cooling has no apparent effect on the action of jejunal mucosal homogenate. Jejunal mucosa apparently contains an inhibitor to gastric acid secretion. Ileal mucosa apparently does not contain an inhibitor to gastric acid secretion. Pyrogens do not appear to be a factor in the action of jejunal mucosal homogenate on gastric acid secretion.

TABLE 2. *Gastric Acid Production (mEq/hr)*

Control Rats	Jejunectomized Rats	Jejunal Mucosal Homogenate
1.3 ± 0.7	3.8 ± 2.3	1.6 ± 0.7

TABLE 3. *Gastric Acid Production (mEq/hr)*

Control Rats	Jejunectomized Rats	Ileal Mucosal Homogenate
1.3 ± 0.7	3.8 ± 2.3	3.7 ± 1.9

TABLE 4. *Gastric Acid Production (mEq/hr)*

Control Rats	Jejunectomized Rats	Cooled Jejunal Mucosal Homogenate
1.3 ± 0.7	3.8 ± 2.3	1.0 ± 0.6

References

1. Caridis, D. T., Roberts, M. and Smith, G.: The Effect of Small Bowel Resection on Gastric Acid Secretion in the Rat. Surgery, **65**: 292, 1969.
2. Copeland, E. M., Miller, L. D. and Smith, G. P.: The Complex Nature of Small Bowel Control of Gastric Secretion. Ann. Surg., **168**:36, 1968.
3. Fischer, J. E., Snyder, S. H., Howard James, J. and Baldessarini, R.: Histamine and Serotonin Metabolism Following Massive Small Bowel Resection. Ann. Surg., **175**:260, 1972.
4. Frederick, P. L. and Craig, T. V.: Effect of Vagotomy and Pyloroplasty on Weight Loss and Survival of Dogs after Massive Intestinal Resection. Surgery, **56**:135, 1964.
5. Landon, J. H. and Baker, W. K.: Gastric Hypersecretion Produced by Massive Small Bowel Restriction in Dogs. Am. J. Surg. Res., **4**:518, 1964.
6. Osborne, M. P., Frederick, P. L., Sizer, J. S., Blair, D., Cole, P. and Thum, W.: Mechanism of Gastric Hypersecretion Following Massive Intestinal Resection. Ann. Surg., **164**: 622, 1966.
7. Reul, G. J. and Ellison, E. H.: Effect of Seventy-five Per Cent Distal Small Bowel Resection on Gastric Secretion. Am. J. Surg., **111**:772, 1966.
8. Ruderman, R. L. and Kamel, I.: Intestinal Control of Gastric Hyperacidity. Surg. Gynecol. Obstet, **134**:637, 1972.
9. Rudick, J., Gajewski, A. K., Fletcher, L., Harkins, H. N. and Nyhus, L. M.: Gastric Inhibtors in Intestinal Secretion Surg. Forum, **17**:295, 1966.
10. Sabsai, B. I.: The Effect of extensive of the Proximal and Distal Portions of the Small Intestine on Canine Gastric Secretion. Biull. Eksp. Biol. Med. (Moscow), **55**:387, 1963.
11. Santillana, M., Wise, L., Schuck, M. and Ballinger, W. F.: Changes in Gastric Acid Secretion Following Resection or Exclusion of Different Segments of the Small Intestine. Surgery, **65**:777, 1965.
12. Thorbjarnarson, B., Rees, J. R., Bjornsson, S., Watkins, G. M. and Martin, K. A.: The Denervated Gastric Pouch of the Rat. J. Surg. Res., **7**:499, 1967.
13. Westerheide, R. L., Elliott, D. W. and Hardacre, J. M.: The Potential of the Upper Small Bowel in Regulating Acid Secretion. Surgery, **58**:73, 1968.

Application of Thyroid Lymphography to Preoperative Localization of Hyperfunctioning Parathyroid Adenomas

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THE TREATMENT OF PRIMARY HYPERPARATHYROIDISM at present is the surgical removal of the hyperfunctioning parathyroid tissue. An accurate preoperative localization of the abnormal hyperfunctioning parathyroids is exceedingly useful, since the number and the position of the parathyroid glands in some cases are extremely variable.[3,4,7,8] Methods used to identify the location of abnormal parathyroid glands before operation include neck palpation, barium swallowing, parathyroid scanning, and thyrocervical arteriography. Localization using any one of these methods has been difficult, therefore, several methods have always been used in combination in our hospital.

This article describes the identification of parathyroid adenomas using thyroid lymphography.

Materials and Methods

Four patients with primary hyperparathyroidism admitted to Nagoya University Hospital for surgical treatment have been studied. All four were females ranging in age from 20 to 55 years. These four patients had solitary parathyroid adenomas. Preoperative localization using thyroid lymphography was compared with macroscopic and microscopic examinations in all cases.

The technique of thyroid lymphography was as follows.

An intradermal skin test or an intravenous test was carried out prior to the procedure to confirm the absence of iodine anaphylactic reaction. The patient lay supine with the shoulders elevated on a pillow and the neck extended. The thyroid gland was palpated and its outline was marked on the skin. One to 1.5 ml. of Lipiodol Ultra-Fluid (Andre Guerbert, France) was injected percutaneously into each thyroid lobe over a period of one minute.

Following removal of the needle, local pressure was applied to the thyroid lobe and the thyrovervical region was observed from various angles under fluoroscopy. Antero-posterior, lateral and oblique radiograms of the lower cervical region were taken at 15, 30, 60 and 120 minutes and 24 hours after injection of contrast medium.

Results

When contrast medium was injected into the normal thyroid gland, it spread diffusely in the injected lobe in a few minutes. The thyroid lobes were visualized as a fine network. The thyroid lymphogram of four patients with the normal thyroid gland are demonstrated in Fig. 1. The parathyroid location was diagnosed as a defect or an impression shadow of the thyroid lymphogram. In each case it was confirmed to be correct by operation.

As shown in Fig. 2 and Fig. 3, the thyroid lobes of the first patient were visualized as a normal fine network and a defect shadow was noted at the postero-lateral aspect of the left lower lobe. An adenoma (1.2 by 1.0 by 0.6 cm. in size, 0.5 grm. in weight) was found at the identified position when this patient was operated upon. In this case preoperative parathyroid scanning and arteriography were unsuccessful. The thyroid lymphograms of the second and third patients offered similar defect shadows in the thyroid contour. The localization was confirmed during surgery in both. Figure 4 presents the antero-posterior view of the thyroid lymphogram of the fourth case. Contrast medium was injected into the

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huge parathyroid adenoma and simultaneously into the thyroid gland. The left thyroid lobe was displaced toward the right by the large left parathyroid tumour. Contrast medium injected into the parathyroid adenoma did not spread diffusely but appeared like oil droplets in water. A large cystic parathyroid adenoma (20.1 grm. in weight) was found at operation. The thyroid contour were clearly visualized on the films exposed at intervals between 15 and 120 minutes after injection. The later the films were exposed, the more cervical lymph nodes were visible. The greatest number of cervical lymph nodes became visible on the film taken at 24 hours after injection. Thus the best timing to obtain the clearest radiogram of the thyroid fine network and surrounding lymph nodes was two hours after the injection of contrast medium.

Discussion

Primary hyperparathyroidism is a relatively rare disease in Japan and only 202 cases have been reported until 1972.[11] Twenty-two patients with primary hyperparathyroidism have been operated upon at Nagoya University Hospital. Of the twenty-two patients, only nine were operated upon during the ten years from 1958 to 1967, while thirteen underwent surgery in the last five years from 1968 to 1972.

When surgery is performed on patients with primary hyperparathyroidism, it is important to succeed with the initial operation. It is difficult to detect the small parathyroid gland upon reoperation. In the re-explored surgical field, the parathyroid glands may be encased in connective tissues and their appearance is easily obscured by minor hemorrhages. Furthermore, injury to the recurrent laryngeal nerve is more likely to occur at re-exploration. Four of twenty-two patients operated upon at Nagoya University Hospital were re-explored. In one of these patients hyperplastic parathyroid glands were resected inadequately; in two, parathyroid adenomas were abnormally located in the mediastinum; and in one only two glands were removed because of hyperplastic glands being misdiagnosed as multiple adenomas in frozen sections.

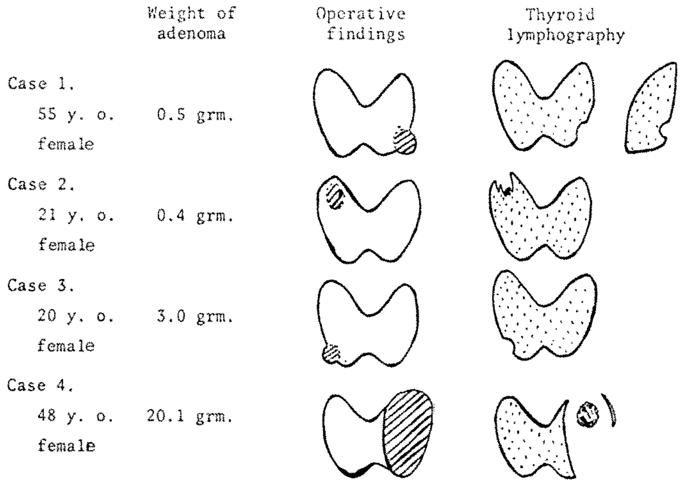

FIG. 1. Demonstration of parathyroid glands by thyroid lymphography. Shadows in figures under operative findings indicate the localization of adenomas of parathyroid glands.
In all four cases thyroid lobes are depressed by parathyroid adenomas, and localizations of the parathyroid adenomas are clearly demonstrated as seen in this schema on thyroid lymphogram.

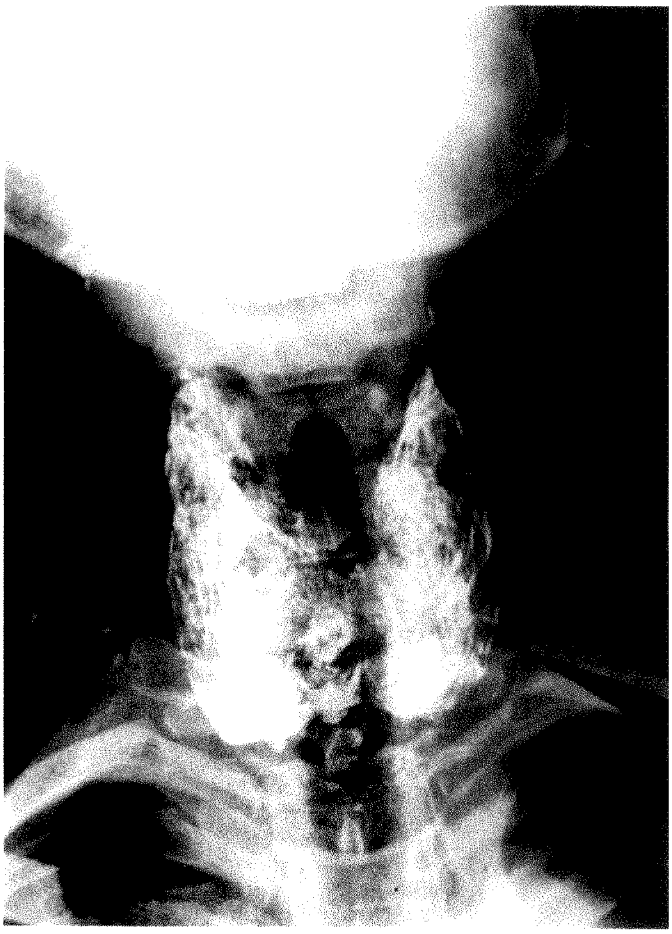

FIG. 2. Antero-posterior view of thyroid lymphogram of Case 1. Contrast medium (Lipiodol Ultra-Fluid 1–1.5 ml./single lobe) was injected to all patients. Photograms were taken at 15, 30, 60 and 120 minutes and 24 hours after the injection of contrast medium respectively. This figure shows the localization of adenomas and the photograms taken at two hours after the injection. Black arrows indicate depressed contour of the thyroid. A parathyroid adenoma (0.5 gm.) was located exactly at this position.

At operation it is important to survey all four parathyroid glands and a biopsy sample should be taken immediately for frozen section before final resection. The histologic diagnosis during the operation is very important, because this examination determines the amount to be resected, i.e. when the biopsy sample is diagnosed as parathyroid adenoma, only enlarged adenomatous glands should be resected and when it is diagnosed as hyperplastic parathyroid tissue, subtotal parathyroidectomy (resection of 3½ glands) shoud be performed. In

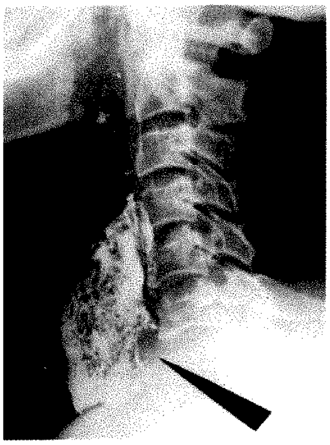

FIG. 3. Lateral view of thyroid lymphogram of Case 1. The legend to this figure is the same as that for Fig. 2.

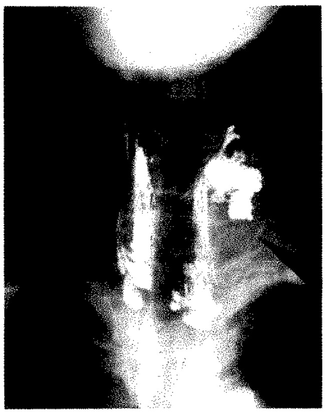

FIG. 4. Antero-posterior view of thyroid lymphogram of Case 4. Contrast medium was injected both into thyroid lobe and into parathyroid cystic adenoma (black arrow). This film was taken two hours after the injection.

some cases the histologic differentiation between adenomatous and hyperplastic parathyroid tissues in frozen sections may be difficult,[5,9] and then macroscopic differentiation during operation is necessary. When one or two parathyroid glands are enlarged and the rest are of normal size and of normal appearance, they may be adenomatous, and when all four glands are enlarged hyperplasia may be present.

The difficulty in determining the size 2) and/or appearance of a parathyroid gland and in removing it renders it very useful to identify a parathyroid gland preoperatively.

Many methods for identifying preoperative localization of abnormal parathyroid glands were compared. In our experiences (Table 1), neck palpation and barium swallowing have proven to be useless. Thyrocervical arteriography may be useful if positive. Very few hyperfunctioning parathyroid glands were correctly demonstrated by parathyroid scintigraphy using ^{75}Se-selenomethionine: i.e. in six of twelve patients positive concentrations of the radioactive selenomethionine were observed by scintigraphy. However, two of them were false positive and in one the concentration was suspected retrospectively after operation. Scintigraphy does not seem to be sufficient to identify the exact location of the parathyroids.

Thyroid lymphography has been used as a technic for visualization of the thyroid gland and cervical lymph nodes.[1,10] In a few minutes after the injection of contrast medium into the normal thyroid of the patient, the thyroid lobe is completely outlined. When an enlarged parathyroid gland depresses the thyroid lobe, it is visualized as a half oval defect or a depressed shadow on the thyroid contour, and when the parathyroid tumor presents in the thyroid lobe, it will be visualized as a round negative shadow. It should be noticed that thyroid lymphography is not a specific technic to identify the parathyroid localization. For example, one must differentiate parathyroid gland from lymph nodes, nodular goiter, and other tumors. However, we believed that thyroid lymphography is a useful method for identification of parathyroid tumors adhering to the thyroid gland, even in the cases of a small parathyroid adenoma. The smallest adenoma identified by this method was 0.4 grams in weight.

When a nodular lesion is in the thyroid, the injection should be made into the thyroid parenchyma itself with careful avoidance of the lesion, then a depression shadow or round negative shadow will be obtained. If the tumor is very large, injection of contrast medium into the thyroid parenchyma becomes difficult, but some information can be obtained by injecting directly into the tumor itself. Application of local pressure on the thyroid lobe is necessary because the defect shadow in the thyroid lymphogram may be camouflaged when a parathyroid gland is in the thyroid lobe and its size is small. Radiograms should be taken after observation under fluoroscopy, because in some angles, the defect shadow may be camouflaged by contrast medium spreading diffusely

TABLE 1. *Detection for Preoperative Parathyroid Localization by Various Methods*

		Results			
Methods	No. of Cases	Any Finding Obtained	Correctly Diagnosed	Misdiagnosed	Postoperatively Found
Palpation	22	6	3	3	1
Barium swallowing	4	0			0
Angiography	5	2	2	0	1
Scanning	12	5	3	2	1
Throid lymphography	4	4	4	0	0

in the thick thyroid gland which covers the thin parathyroid. This test should be performed after thyrocervical arteriography, because contrast medium remains in the thyroid lobe for about ten days. Though no severe complications have been encountered,[6] the iodine anaphylactic test should be carried out before the procedure.

Summary

Thyroid lymphography was performed on four patients to identify the location of hyperfunctioning parathyroid adenomas. It proved to be useful in all cases. In three cases the parathyroid glands were visualized as defects or depressed shadows in the thyroid contour. In one case contract medium was injected both into the adenoma and the thyroid lobe.

It is concluded that thyroid lymphography is one of the most helpful methods available to identify the parathyroid adenoma preoperatively.

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References

1. Beales, J. S. M., Nundy, S., *et al.*: Thyroid Lymphography Brit. J. Surg., **58**:168, 1971.
2. Black, B. M.: Problems in the Treatment of Hyperparathyroidism. S. Clin. North Am., **41**:1061, 1961.
3. Bruining, H. A.: Surgical Management of Hyperparathyroidism. Netherlands, Royal Van Glrcum, 52, 1972.
4. Castleman, B.: Atlas of Tumor Pathology. Section IV (Tumor of Parathyroid Glands), Washington, A.F.I.P., 24, 1952.
5. Cope, O., Barnes, B. A. *et al.*: Vicissitudes of Parathyroi Surgery. Ann. Surg., **160**:1017, 1964.
6. Esaki, H. and Tani, T.: Thyroid Lymphography. Surg. Ther (Osaka), **27**:603, 1972 (in Jap.)
7. Gilmour, J. R. and Martin, W. J.: The Gross Anatomy of th Parathyroid Glands. J. Pathol., **46**:133, 1938.
8. Gilmour, J. R.: The Embryology of the Parathyroid Glands J. Pathol., **44**:431, 1937.
9. Hoff, R. C.: Causes of Recurrent Hypercalcemia after Parathyroidectomy for Primary Hyperparathyroidism. Ann. Surg, **173**:884, 1971.
10. Matoba, N. and Kikuchi, T.: Thyroidlymphography. Radiolog **92**:339, 1969.
11. Sonoda, T., Takeuchi, M., *et al.*: Parathyroid Tumors. Jap J. Clin. Med., **30**:828, 1972. (in Jap.)

Management of Transmural Peptic Strictures of the Esophagus

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PEPTIC STRICTURES complicating reflux of gastric juice into the esophagus continue to provoke debate regarding proper surgical management.

Thal's[16] fundic patch procedure, alone, or combined with Nissen's[10] fundoplication, as advocated by Woodward and his associates,[17] appear to be promising approaches to the problem.

Recent enthusiasm for these operations prompted us to review our results with two "older" procedures used in treating transmural strictures.

Between 1951 and 1969, 18 patients underwent esophagogastric resection with jejunal interposition[9] or gastric bypass[3] because of peptic esophagitis with stricture. This group represents about 15% of all patients with distal esophageal stricture seen at the New York Hospital during this period.

Clinical Material

The 18 patients included in this study underwent esophagogastric resection because of: (1) failure to restore esophageal patency by dilation, (2) repeated bouts of hemorrhage, or (3) fear of malignancy.

Esophagojejunostomy with gastric bypass was employed in eight patients following resection of the stricture and the esophagogastric junction. In ten other patients, gastrointestinal continuity was restored by interposition of a segment of jejunum between the esophagus and gastric remnant.

Group I: Gastric Bypass

Gastric bypass (Fig. 1) was carried out in eight patients with distal esophageal strictures. Among the eight patients, five were women and three were men. Their ages ranged from 29 to 74 years. In five of these patients, the strictures had resulted from treating esophageal achalasia by sphincter destroying procedures (Table 1). Among the other three patients, inflammatory transmural fibrosis resulted from gastric reflux in association with hiatus hernia in two, and scleroderma in one.

Prior to gastric bypass, six of the eight had lost weight (average amount, 16 pounds); all had experienced bouts of complete obstruction and four had bled, one massively.

Group II: Jejunal Interposition

Jejunal interposition with esophagojejunal and jejunogastric anastomoses (Fig. 2) was employed in ten patients subsequent to esophagogastric resection. There were five women and five men in this group. The age range was 37-73 years.

A too generous cardiomyotomy (Heller procedure) for achalasia had produced free reflux and subsequent peptic stricture in two of these patients. Wendel's cardioplasty accounted for reflux esophagitis in two additional patients with achalasia (Table 2).

Hiatus hernia with reflux had resulted in strictures in four patients who underwent jejunal interposition, two

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of whom had undergone three previous operative attempts to correct their esophageal stenosis. A previous jejunal interposition had been attempted in one (Table 2).

In one patient, a 42-year-old woman maintained flat in bed following an abdominal procedure complicated by ileus, prolonged nasogastric intubation resulted in a stricture at the esophagogastric junction. Dense mediastinitis occurred after a perforation of the esophagus during attempted dilatation of the stricture. Further attempts at dilatation were therefore abandoned (Table 2).

Advanced scleroderma of the gastrointestinal tract with esophageal involvement set the stage for reflux with a full-thickness esophageal burn in a 36-year-old woman. Total esophageal obstruction developed and was treated by jejunal interposition (Table 2).

Life-threatening hemorrhage had occurred in two of the nine patients. Marked weightloss had occurred in five (average amount, 18 pounds), and all had a history of episodes of complete obstruction.

Immediate Results of Operation

There were no hospital deaths in either group. Major complications were encountered in only two patients. Empyema thoracis occurred in one patient in Group I and intrathoracic hemorrhage (necessitating thoracotomy) in one patient in Group II.

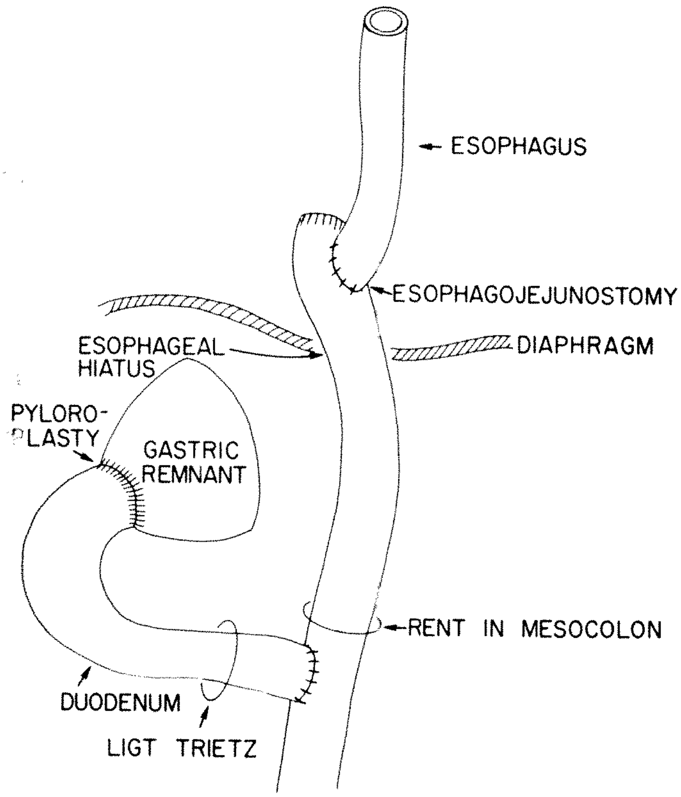

FIG. 1. Method of gastric bypass for stenosing peptic esophagitis employed in eight patients.

TABLE 1. *Etiologies Encountered Among Eight Patients Undergoing Esophagogastrectomy and Gastric Bypass for Stenosing Peptic Esophagitis*

Esophageal Stricture Associated with or Following	Number of Patients
Cardioplasty for achalasia	3
Achalasia with reflux after forceful dilatation	1
Cardiomyotomy for achalasia (Heller)	1
Scleroderma	1
Hiatus hernia with reflux	2

Ulcers were noted in the pathology specimens in five of the eight.

Late Results of Operation

Patients in either group who have maintained the ability to swallow without discomfort, do not require dilatation, are without bouts of regurgitation, and are free from respiratory complications, are termed good results.

Those patients developing dysphagia, inanition, anastomotic stricture requiring re-operation or dilatation, or respiratory complications are termed poor results.

Each patient underwent at least one barium swallow six months to one year post-operatively. Esophagoscopy was carried out on anyone developing dysphagia, nocturnal substernal distress, radiographic evidence of anastomotic stricture, or those who would volunteer.

The appearance of a macrocytic anemia alone, though undesirable, was not considered in and of itself a poor result unless accompanied by other complications.

Group I

All patients who underwent gastric bypass initially lost weight (Table 3). However, a plateau was reached in all instances below which no further weightloss occurred. One patient is, currently, frankly obese.

A macrocytic anemia responsive to parenteral cyanicobalamin therapy occurred in four patients followed ten years or longer (Table 3).

TABLE 2. *Etiologies Encountered Among Ten Patients Undergoing Esophagogastrectomy and Jejunal Interposition for Stenosing Peptic Esophagitis*

Esophageal Stricture Associated with or Following	Number of Patients
Cardiomyotomy for achalasia (Heller)	2
Cardioplasty for achalasia (Wendel)	2
Prolonged nasogastric intubation	1
Hiatus hernia with reflux*	4
Scleroderma	1

* Two patients had three previous operations for esophagitis. Esophageal ulcers were encountered among seven patients undergoing jejunal interposition for peptic stricture.

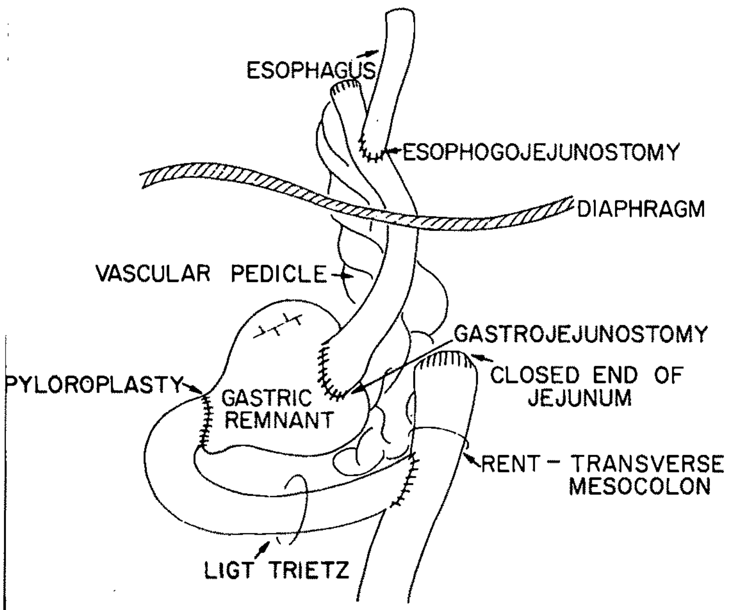

FIG. 2. Method for jejunal interposition for stenosing peptic esophagitis employed in ten patients.

An anastomotic stricture was evident in one 56-year-old woman three months following gastric bypass. Revision of the esophagojejunostomy and gastrostomy were carried out. Subsequently, this patient continued to have difficulty gaining weight. A Schilling Test was positive when she presented with marked anemia seven years post-operatively. Esophagoscopy and a barium swallow performed at that time did not demonstrate a stricture. She was lost to follow-up five years later. This patient represents the poorest result among the eight who underwent gastric bypass (Patient four, Table 3).

During the follow-up period, four patients died. Patient number three (Table 3) expired of complications of cerebral arteriosclerosis 20 years after gastric bypass. Except for the macrocytic anemia, she did well.

Dysphagia and a sensation of fullness in the throat occurred in a 46-year-old man, ten years after cardioplasty for achalasia and five years after gastric bypass. After a symptom free interval of four years, he was found to have a carcinoma of the esophagus, not resectable at thoracotomy (Patient six, Table 3).

The seventh patient in Table 3, a 74-year-old male, expired in a Veterans Administration Hospital three years post-operatively. He was asymptomatic with regard to his esophageal disease until his death.

The final patient in Table 3 died from carcinoma of the lung 14 years after gastric bypass. He had no gastrointestinal problems at the time.

Discounting the occurrence of a macrocytic anemia, seven of eight patients undergoing gastric bypass for esophageal strictures, have done well for follow-up periods of from two to 20 years.

Group II (Jejunal Interposition)

Poor late results were observed in three patients in Group II (Table 4). In all three, anastomotic strictures developed at the site of the esophagojejunal anastomosis. Massive bleeding (presumably from the anastomotic site) occurred in one of the three.

An anastomotic stricture requiring frequent dilatation accounted for the poor result in the first patient in Table 4. He did not undergo concommitant pyloroplasty at the time of jejunal interposition and died from complications of an acoustic neuroma four years post-operatively.

Suspected bleeding from an esophagojejunal stricture occurred in a 75-year-old woman (Patient five, Table 4), six years after interposition. She is still living and has moderate dysphagia.

Re-operation for anastomotic stricture was carried out in a 53-year-old woman four months following jejunal interposition. Subsequent to this operation, she continued to require periodic dilatation. This patient currently has inanition due to problems surrounding her chronic, heavy, ingestion of alcohol (Patient seven, Table 4).

Three late deaths have occurred among the ten patients who underwent jejunal interposition after esophagogastric resection. One patient died four years post-operatively from complications of an acoustic neuroma (Patient one, Table 4).

Another died at 83 years of age, of causes incident to her age, ten years after jejunal interposition (Patient four, Table 4). Three years prior to this patient's death, an upper gastrointestinal series demonstrated well func-

TABLE 3. *Late Results of Gastric Bypass for Esophageal Stricture*

Patient Number	Sex	Age at Operation	Length of Followup	Late Complications	Result
1	F	37 years	20 years	Macrocytic anemia	Good
2	F	29 years	Ten years then lost	Macrocytic anemia	Good
3	F	59 years	Expired 20 year after operation	Macrocytic anemia	Good
4	F	56 years	Lost after 12 years	Anastomotic stricture Macrocytic anemia	Poor
5	F	52 years	Two years	None	Good
6	M	40 years	Expired five years after operation	None	Good
7	M	74 years	Expired three years after operation	None	Good
8	M	57 years	Expired 14 years after operation	None	

TABLE 4. *Late Results of Jejunal Interposition for Esophageal Stricture (Group II)*

Patient Number	Sex	Age at Operation	Length of Follow-up	Late Complication	Status	Overall Result
1	M	66 years	Four years	Stricture	Dead	Poor
2	F	37 years	Three years	None	Alive	Good
3	M	50 years	12 years	None	Alive	Good
4	F	73 years	Ten years	None	Dead	Good
5	F	69 years	12 years	Stricture Hemorrhage	Alive	Poor
6	F	40 years	Four years	None	Dead	Good
7	F	53 years	Eight years	Stricture with reoperation	Alive	Poor
8	M	61 years	Seven years	None	Alive	Good
9	M	54 years	Four years	None	Alive	Good
10	M	48 years	One year	None	Alive	Good

tioning jejunogastric and jejunoesophageal anastomoses without evidence of stricture.

The third late death occurred in a 44-year-old woman with extensive gastrointestinal involvement due to scleroderma (Patient six, Table 4). She had chronic malabsorption syndrome and died from inanition. The interposed jejunal segment functioned well until the time of death without evidence of stricture formation.

In summary, seven of ten patients have done well for periods of one to 12 years after jejunal interposition.

Discussion

Current methods of hiatus hernia repair, including Belsey's[11,15] Mark IV repair, Nissen's[10] fundoplication, and Hill's[7] repair employing the preaortic fascia, are all apparently superior to those used in the past. We believe these methods are applicable to patients having peptic esophagitis with stricture, provided the esophageal stenosis is not due to circumferential destruction of muscle.

In many large surgical series reviewed,[4,11,15,18] there remain a small group of patients for whom resection of the stricture was the only effective method of treatment. In most instances, these are patients who have undergone previous surgical attempts to relieve their esophageal stenosis and have ultimately sustained full thickness, circumferential burns of the esophageal wall.[14]

Thal[16] and Thomas, *et al.*[17] have treated this group of patients with some success. Allison[1] states that he has about fifty such patients under his care who have undergone jejunal interposition and have done well.

Interestingly enough, gastric bypass[3] compares favorably with jejunal interposition[9] as a method of restoring gastrointestinal continuity in the small series of patients presented. The late occurrence of macrocytic anemia nd the seemingly "unphysiologic" nature of the procedure have lead to a lack of use and interest.

Substitution of an interposed segment of jejunum for the esophagus[9] may be fraught with late complications.[2,13,19] But in many instances, the segment may function for long periods of time without difficulty as brought out in our study and in Hase's[5] report on Roux's original case.

In a similar fashion, late complications have been described in using the colon[12,13] or the stomach[6,8] for an esophageal substitute.

The combined fundic patch fundoplication operation[17] may be the answer to the difficult problem of a full-thickness esophageal burn with resultant fibrosis. However, the results of this procedure must be critically compared overall a long period of time to those obtained with "older" procedures.

Summary

Esophagogastric resection with either jejunal interposition (ten patients) or gastric bypass (eight patients) was carried out in 18 patients with severe esophageal strictures encountered between 1951 and 1969.

There were no operative deaths and the overall results were considered to be good in 13 of the 18 patients over a follow-up period extending from two to 20 years.

References

1. Allison, P., in a discussion of: Hill, L. D., Gelfand, M. and Bauermeister, D.: Simplified Management of Reflux Esophagitis with Stricture. Ann. Surg., **172**:638, 1970.
2. Bansmer, G., Bill, A. H., Jr. and Crystal, D. K.: Two Cases of Perforated Peptic Ulcer Occurring as Postoperative Complications of Esophagectomy with Jejunal Interposition. Ann. Surg., **149**:586, 1959.
3. Barnes, W. A. and Redo, S. F.: Evaluation of Esophagojejunostomy in the Treatment of Lesions of the Esophagogastric Junction. Ann. Surg., **146**:224, 1957.
4. Brindley, B. V. and Wangsanutr, L.: Surgical Treatment of Stricture of the Esophagus Associated with Hiatal Hernia. Ann. Surg., **173**:649, 1971.
5. Hase, O. and Habif, D. V.: Ultimate End Result of the First Prethoracic Jejunal Esophagoplasty of Ce'sar Roux (1906). Surgery, **51**:694.
6. Heimlich, H. J.: Elective Replacement of the Esophagus. Brit. J. Surg. **53**:913, 1966.
7. Hill, L. D., Gelfand, M. and Bauermeister, D.: Simplified Management of Reflux Esophagitis with Stricture. Ann. Surg., **172**:638, 1970.

8. Kirkpatrick, J. R. and Allbritten, F. F., Jr.: A Gastropleural Fistula 12 Years Following Gastric Interposition for Carcinoma of the Esophagus. J. Thorac Cardiovasc. Surg., **58**:769, 1964.
9. Merendino, K. A. and Dillard, D. H.: Concept of Sphincter Substitution by Interposed Jejunal Segment for Anatomic and Physiologic Abnormalities at Esophago-gastric Junction. Ann. Surg., **142**:486, 1955.
10. Nissen, R.: The Treatment of Hiatal Hernia and Esophageal Reflux by Fundoplication. *In* Hernia. Nyhus, L. M. and Harkins, H. N., editors. Philadelphia, J. B. Lippincott Co., 1964.
11. Pearson, F. G., Langer, B. and Henderson, R. D.: Gastroplasty and Belsey Hiatus Hernia Repair. J. Thorac. Cardiovasc. Surg, **61**:50, 1971.
12. Raia, A., Gama, A. G., Pinotti, H. W. and Rodriques, J. J. G.: Diverticular Disease in the Transposed Colon Used for Esophagoplasty: Report of Two Cases. Ann. Surg., **177**:70, 1973.
13. Rapant, V., Kralik, J. and Doubravsky, J.: Peptic Ulcer in the Jejunum or Colon Following Esophageal Replacement. Int. Surg., **54**:126, 1970.
14. Skinner, D. B., in a discussion of: Hill, L. D., Gelfand, M., and Bauermeister, D.: Simplified Management of Reflux Esophagitis with Stricture. Ann. Surg. **172**:638, 1970.
15. Skinner, D. B. and Belsey, H. R.: Surgical Management of Esophageal Reflux and Hiatus Hernia. J. Thorac. Cardiovasc. Surg., **53**:34, 1967.
16. Thal, A. P.: A Unified Approach to Surgical Problems of the Esophagogastric Junction. Ann. Surg., **168**:542, 1968.
17. Thomas, H. F., Clarke, J. M., Rayl, J. E. and Woodward, E. R.: Results of the Combined Fundic Patch Fundoplication Operation in the Treatment of Reflux Esophagitis with Stricture. Surg. Gynec. Obstet., **135**:241, 1972.
18. Urschel, H. C., Jr. and Paulson, D. L.: Gastroesophageal Reflux and Hiatal Hernia. J. Thorac. Cardiovasc. Surg., **53**:21, 1967.
19. Witt, C. B. and Averbook, B. D.: Intestinal Obstruction Following Jejunal Interposition Operation. Arch. Surg., **93**:498, 1966.

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